National Institute on Drug Abuse

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Problems of Drug Dependence 1995: Proceedings of the 57th Annual Scientific Meeting

The College on Problems of Drug Dependence, Inc.

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Problems of Drug Dependence,

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Editor:

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Virginia Commonwealth University

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IN MEMORIAM

JULIAN E. VILLARREAL

1937-1995

Dr. Julian E. Villarreal died of liver cancer on January 17, 1905.

Julian, as he was known to all of his many friends and colleagues, was born in Mexico City on April 10, 1937. Upon receiving the M. D. degree from the University of Mexico in 1960, he traveled north to Ann Arbor to enter the graduate program of the Department of Pharmacology of the University of Michigan. Julian completed a doctoral research project under the supervision of Dr. Edward Domino. Before Julian had a chance to write and defend his doctoral dissertation, Dr. Maurice Seevers, Chairman of the Department, tapped him to take over the "monkey laboratory" that Seevers had established years earlier to study the phenomenon of physical dependence to opiate analgesics. As an Instructor, Assistant Professor, and Associate Professor of Pharmacology, Julian directed the research activities of the laboratory, studying opiate tolerance and physical dependence in rhesus monkeys and other laboratory animals. Under the auspices of the Committee (now College) on Problems of Drug Dependence, he screened hundreds of coded compounds for their capacity to produce morphine-like physical dependence in the rhesus monkey. Julian eventually received the Ph.D. degree from the University of Michigan, after writing and defending a doctoral dissertation on the original opiate research that he performed while he was director of the laboratory.

Julian returned to Mexico City with his growing family in the early 1970s. Over a ten year period he was affiliated with the Miles Institute of Experimental Therapeutics, first as Director of Behavioral Pharmacology, then as Director of the Institute. Subsequently, he returned to the National University of Mexico as Professor of Pharmacology, finishing his career as Chairman of the Department. He took a two year leave from the University to serve the people of Mexico as Director General of the Drug Regulation Oftice, Mexican Health Secretariat, an office analogous to the Commissioner of the Food and Drug Administration in the United States.

Julian will be remembered for his innovative research and his enviable ability to theorize. He introduced pupilography and measurement of core body temperature as means of quantifying the acute effects of opiate drugs and the intensity of opiate withdrawal in monkeys. He developed a paradigm of aversive social interaction between monkeys in order 10 study the effects of drugs on punished behavior in a manner that closely paralleled situations likely to occur with a human subject population. As the new class of mixed-

action opioids--drugs with both agonist and antagonist properties--began to gain prominence, Julian played a leading role in characterizing in the monkey the then-unique pharmacology of these compounds. He published some of the earliest review articles describing the reduced physical dependence potential of mixed-action opioids relative to morphine, and helped organize international scientific meetings to promote exchange of information and ideas about these drugs. In his more recent publications, Julian focused on developing theoretical constructs for the states of opioid dependence and withdrawal.

Julian Villarreal was a true scholar who could address with equal cogency and aplomb the major social issues of the time and how seasonal variations in the make-up of alfalfa might affect responses of the isolated guinea-pig ileum to opiate drugs. He was a delightful and supportive mentor and colleague. We will miss his insightfulness, his self-deprecating manner, his unflaggingly cheerful demeanor, and his friendship. We extend our sincerest condolences to Julian's lovely and loving family.

Stephen G. Holtzman
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Emory University School of Medicine
Atlanta, Georgia

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Department of Pharmacology
University of Michigan Medical School
Ann Arbor, Michigan

IN MEMORIAM

LEWIS JOSEPH SARGENT

1909-1995

Dr. Lewis Joseph Sargent, an organic chemist at the National Institutes of Health from 1941-1973, died April 27, 1995.

Dr. Sargent was born in Brooklyn, New York, on October 27, 1909, of Russian (immigrant) parents. He received the B. S. and M. S. degrees from Brooklyn Polytechnic Institute in 1932 and 1935. He traveled to the British Isles for further graduate study and was awarded a Ph.D. in organic chemistry from the University of Edinburgh in 1938, under the mentorship of Professor George Barger.

Upon returning to the States, Lew, as he was familiarly known, was awarded a one year National Research Council fellowship to do research at the University of Virginia with Dr. Lyndon Small, Chief of the Drug Addiction Laboratory, sponsored by the National Academy of Sciences. Thereby, in effect, began his association with the Committee on Drug Addiction which ultimately evolved into the present College on Problems of Drug Dependence (CPDD) through the Committee on Drug Addiction and Narcotics (1974) and the Committee on Problems of Drug Dependence (1965). He was then Research Associate at Johns Hopkins (1939-1941) after which he again joined (March 1941) the Small, Erich Maseltig-Nathan Eddy team whose research endeavors had been acquired by the National Institute (later Institutes) of Health (NIH), July 1, 1939.

Sargent's research during World War II was on the synthesis of new anti-malarials with emphasis on acridines, fluorenes, and nucleosides. In 1946, he returned to his first love in science, the structure of alkaloids including morphine derivatives (metopon, *e. g.,* the efficacious analgesic developed by Small, et al.,) and rearrangement products.

Sargent served as a committee member of CPDD from 1969-1973, the latter, the year he retired from NIH with the rank of Scientist Director (PHS Commissioned Corps). He had been in civil service from 1941-1948, and was Assistant Chief (to Bernhard Witkop) of the Laboratory of Chemistry, 1958-1973.

He is survived by his wife, Eleanor, whom he married in 1947, and by a son, Robert.

E. L. May

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IN MEMORIAM

HARRIS ISBELL

1910-1994

Dr. Harris Isbell died December 24, 1994, at the age of 84. He graduated from the University of Arkansas with honors in 1931 and from the Tulane University College of Medicine with honors in 1934. He served internships at Charity Hospital, New Orleans from 1934-1935 and at the U. S. P. H. S. Hospital in Lexington, Kentucky from 1935-1936. He entered the United States Public Health Service in 1936. From 1939 to 1944, he investigated nutritutional disease at the National Institutes of Health in Bethesda, Maryland and the University of Georgia College of Medicine. In 1944, he was assigned to the Addiction Research Center Hospital in Lexington, Kentucky and was Director from 1945 until 1963.

At the Addiction Research Center, Dr. Isbell proved that methadone had dependence liability similar to that of morphine but was useful in treating withdrawal from opiates. He was the first lo study narcotic antagonists in man and showed that nalorphine could be used to diagnose physicaI dependence. He and his associates proved that barbiturates and ethanol created a kind of physical dependence in man characlerized by convulsions and delirium on withdrawal and developed a method of treating this type of physical dependence. Dr. Isbell was among the first to study LSD. He proved that chronic administration of LSD caused a tolerance and cross-tolerance to psilocybin and mescaline. Dr. Isbell showed that delta-9-tetrahydrocannabinol was the compound in marijuana that accounts for most of the effects.

At the Addiction Research Center, he established and developed new laboratories, such as neuropharmacology, neurochemistry, drug metabolism, sociology, and epidemiology. He served as mentor to many young scientists who established internationally recognized research programs. Many will remember Harris Isbell for his wisdom, intellect, kindness, and support in facilitating their scientific activities and careers.

In 1963, Dr. Isbell left the Public Health Service and became Professor of Medicine and Head of the section on Clinical Pharmacology, Department of Medicine, University of Kentucky College of Medicine. He won the Burroughs-Wellcome Foundation Award in Clinical Pharmacology in 1963. From 1966 to 1968 he was acting Chairman of the Department of Medicine.

Dr. Isbell contributed over 100 articles to medical and scientific literature. He was the first Harold Cummins Distinguished Lecturer at Tulane University of Medicine in 1969 and the ninth Baxter-Travenol Lecturer,

American Society of Anesthesia and Analgesia in 1971. He gave the second Nathan B. Eddy Memorial Lecture of the National Research Council's Committee on Problems of Drug Dependence in 1985, and was the George Minot Lecturer at the American Medical Association Section on Clinical Pharmacology.

Dr. lsbell was active in many scientific societies including the American College of Physicians, the American Society of Pharmacology and Experimental Therapeutics, the American Society of Clinical Pharmacology, the American College of Neuropsychopharmacology, and the College of International Psychopharmacology. He served on numerous national and international committees dealing with drug dependence.

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COLLEGE ON PROBLEMS OF DRUG DEPENDENCE PRESIDENTIAL ADDRESS 1995. EVIDENCE-BASED TREATMENT AND PREVENTION: RESEARCH FOR THE HEALTH OF THE PUBLIC

E. M. Sellers

Departments of Pharmacology, Medicine and Psychiatry, University of Toronto; and the Addiction Research Foundation, Toronto, Canada.

Nam et ipsa scientia potestas est
(Knowledge is power)

Sir Francis Bacon

In a time of turbulence and change, it is more true than ever that knowledge is power.

John Fitzgerald Kennedy

> *Let a man profess to have discovered some new Patent Powder Pimperlimplimp, a single pinch of which being thrown into each comer of a field will kill every bug throughout its whole extent, and people will listen to him. with attention and respect. But tell them of any simple common-sense plan, bused upon correct scientific principles, to check and keep within reasonable bounds the insect foes of the farmer, and they will laugh you to scorn.*
>
> *Benjamin Walsh The Practical Entomologist (1866)*

The thesis of my presentation today is that science and research, and drug abuse research and treatment in particular, are seriously threatened by the current shifts in public attitude and political climate. I will argue that attitudes concerning the nature of drug dependence in society and even among health professionals makes us especially vulnerable. It is my view what the College can best help offset these ominous trends by being an advocate and leader for evidence-bassed prevention, treatmeut and policy initiatives. Preferably this will be in the form of critically and objectively compiling and reporting the scientific literature and encouraging the conduct of large controlled trials in real settings of care. Such leadership will help lo move our field from one reliant on small scale trials of limited generalizability to one in which widespread prevention and treatment can be based on a credible broad base of evidence. In my opinion, much of the research to date is difficult for the public and politicians to translate into improvement in the health of the public as measured in economic, individual or social terms. The research priorities of funding agencies may need reshaping in order to encourage some of the approaches I will propose.

A number of rapidly evolving changes in society's view of science and research should be attracting the attention of scientists in our field.

First, political and social movements are gaining power based on the populist appeal of "enfranchisement", "consultation" and "process". These euphemisms should be of concern to most scientists because they ignore rational thought and the high standards upon which important intellectual and incremental knowledge have been achieved in society. This is of course not the first time science has been under attack (nor will it be the last)--a recent article in the New York Times (Browne, 1995) reminded the reader that scientists have occasionally had to defend themselves from forces anathema to rational thought and that a soldier of the Roman Empire killed Archimedes!

Second, the vigorous efforts to reduce national and state (provincial) debt results in budget cuts lo both legitimate 'areas of waste (*e.g.* over-utilization of health or social services) and areas of low political risk (*e.g.*

health and mental health research). Unfortunately, the evolution of health services delivery is proceeding under the banner of financial ratianalization and cost-effecliveness. However, at present the only outcome measure that can be assessed with confidence is cost. In many cases the most cost-effective form of treatment is not known and comprehensive measures of health care outcomes are too poorly developed to be useful. The impact of managed care on research could be quite adverse unless we help to define the agenda of what research is important and to then perform such research (Kassirer, 1995).

Third, there has been an ascent of so called "post-modernist" critics of science who contend that truth in science depends on one's point of view, not any absolute content--n kind of experiential or sociologic soup theory of knowledge. Professor Paul Gross, Director of the Center for Advanced Studies at the University of Virginia, is reported to have said (Flint, 1995).

> "Criticizing science has become a new industry. There's a distinguished tradition of the history of science and the philosophy of science, but now sociologisls, feminists and literary theorists have taken it over. This is all the consequence of the revolutions of the sixties--the idea that everyone has their own way of knowing things."

Fourth, the ready availability of information (much of it of uncertain quality) on the Internet has made "knowledge" readily available to virtually anyone. As a result it is easy for anyone to become, if not all expert at least a "channel" of compiled information, and to create the halo of "expertness" at least to the non-expert. The public's appetite for such information seems insatiable.

One reason that our field is particularly vulnerable lo the forces I have noted is because of the unusually wide divergence of attitudes and beliefs about the nature of drug abuse and dependence and its treatment. Table 1 summarizes two studies which sought to understand the beliefs and attitudes of the general public and a group of physicians, nurses and psychologisls involved in conlinuing education courses.

Table 1. Comparison of Percent General Public and Health Professionals Endorsing Etiologic Concepts of Drug Dependence

	Index Drug					
	Alcohol		Tobacco		Cocaine	
Construct	General Public	Health Professionals	General Public	Health Professionals	General Public	Health Professionals
Addiction	90	88	71	73	87	89
Disease	80	67	33	38	51	56
Habit	27	27	76	56	50	36
Sin	21	29	13	29	52	36

Tabulated are the percent of each group agreeing or strongly agreeing with the concept. General Public N = 189-194 (Cunninghan *et al.,* 1994). Health Professionals N = 45 (Romach *et al.,* 1995 unpublished observations).

Particularly notable among these data are the wide diversity of views in both groups, the differences among the substances and the very similar patterns between the general public and the health professionals surveyed. While health professionals are less likely to endorse alcoholism as a disease they are still more likely to see cocaine dependence as a disease. A substantial number of both groups see the abuse of these substances as a "sin". This is particularly the case with cocaine. Because all behavioural pharmacological evidence suggests the underlying principles of drugs as reinforcers applies to each of These, the diversity of views about what is behind these behaviours must reflect quite strongly held prejudices. The diversity probably also explains why new "cures" and quick fixes can so easily capture the momentum and enthusiasm of a substantial number of

individuals at anytime. Therefore our field, probably more than others, is likely to be susceptible to fads, fashions and political whim because of the lack of a strongly held central tendency in beliefs.

In addition, the potential impact of divergent attitudes and beliefs on treatment could include: lack of priority for research, prevention and treatment; an acceptance of lower standard of research, prevention and treatment than in other areas; increase in the need for consensus-based processes rather than evidence-based ones; a basis of misunderstanding, conflict, disagreement and resistance among researchers, treatment staff and administrators; and an acceptance of variable quality of information, and assessment and treatment.

This diversity in attitudes and beliefs is fertile ground for the seeds of the current political and social movements. This synergy is particularly bad news for the drug abuse and dependence research and treatment world at least judging by some of the things going on in Canada.

Over the past five years in Canada we have seen provincial addictions agencies across the country disbanded or integrated into other government services along with a marked reduction in research. The largest and most prestigious of these, the Addiction Research Foundation of Ontario has undergone successive budget reductions for more than five years and has changed the direction of its commitment away from the areas upon which it has built its scientific reputation; namely, evidence-based research concerning the epidemiology, consequences, bio-behavioural basis of dependence and the development of new treatments. This shift has occurred over only a short period of time and been possible in this organization because its mandate encompasses three diverse goals: research, community development and treatment. While in an ideal world the combination of these goals in a single organization should be preferred, in practice the mixing of the very different value systems of each results in substantial conflict and organizational turinoil. In response to a provincial government which has been philosophically populisl, leadership in the Foundation sympathetic to community development and observational and theoretical research have held sway, and rigorous evidence-bad research has become a lesser priority.

The recent election of a conservative government in the province of Ontario may alter the driving philosophy behind government. However, the new Premier of the province has already been referred to as "the Newt Gingrich" of the North (Arizona Republic yesterday, [June 10, 1995]), in reference to his tough fiscal position! Hence, if budget cuts are applied to research as are being proposed in the United States, fiscal change rather than principles and priorities may result in even more radical changes in the Foundation. The long-term consequences to the Foundation's research are difficult lo judge at this time. Fortunately, several new young scientists have recently been hired who may serve as a nidus for new research initiatives. Unfortunately these are not good times in any country for young scientists starting out and it is likely that the current times will discourage even more from entering the field. However, it would not be surprising IO see an increasing reliance on the development of less costly descriptive inquiry. The need by media and governments for immediacy (as distinct from that which is peer-reviewed and evidence-based) would certainly favour popular observational studies and direct-to-consumer type of "research" reporting.

The changes at the Foundation, dressed up in bureaucratic euphemisms ("right-sizing", "delayering", etc.) are not atypical. One can hear similar accounts across North America. The reasons are virtually all the same and derive from organizations responding to the changing context and political world in which we are now immersed. The justitications are all more or less the same, namely being responsive to what the public wants. The issue, of course, is not what is wanted but what is needed for society in the long-term. Hopefully, sufficient wisdom and vision will prevail that will allow organizations to not over-react and to thereby weather the current stormy times and retain their research and educational infra-structure essential for future scholarly contributions.

Another development which should be attrracting our attention and is highly relevant to the interface of research and treatment in our field is the widespread development of practice guidelines. While on the surface such initiatives seem commendable, I believe we should be concerned that they represent, on balance, a threat to evidenced-based treatment and to research.

As you know, developing such guidelines is not particularly new. For more than SO years this has been one way to nominally encourage health care providers to make better or at least more consistent decisions. Recently the number of organizations developing such guidelines has increased tremendously. In 1992 it was estimated that there were more than 45 physician groups alone creating more than 1,500 sets of guidelines.

There is no unanimity about the merit of practice guidelines. Those who are advocates for guidelines claim they: assist patients to make informed decisions; reduce inappropriate care; increase cost-effectiveness; assist third party utilization, performance and reimbursement review; and improve quality of care--while critics argue they: are cookbook and stille innovation; are bureaucratic and expensive to maintain and increase costs; reduce research activity where it is needed; make clinical care boring; and decrease competence. Irrespective of perspective, there seems to be agreement that the reasons guidelines can fail is because of poor adoption strategy and the lack of incentives to use them, including failure to have the users feel they own the guidelines.

From my perspective, the principal weaknesses of most practice guidelines are that the analyzed database is not in the public domain, the rigor of the analysis of the data review is weak and the final document is often based on a consensus process which involves compromise, trade-offs and makes the best of what is known. Such a process is not evidenced-based treatment or prevention. In many cases it is somewhere between a protracted opinion poll and a compilalion of practical guesses.

My recent involvement in a consensus guideline process forced me to critically re-evaluate a line of research; namely, the treatment of alcohol withdrawal, in which I had been involved for almost 20 years. I concluded that only the most modest guidelines were possible because of the lack of proper trials of sufficient size that addressed questions that patients, clinicians, administrators and third party payers would like answered. For example, what is the most cost-effeclive out-patient treatment of alcohol withdrawal in community settings. In simple words--the data were not up to the task. This did not deter the process from proceeding and draft guidelines are still being circulated!

This is the case for much of the research relevant to drug abuse treatment. I very much enjoyed the comment of a leading member of the College, whose admonition to an audience after presenting the results of an open label trial showing impressive improvement in patient outcomes said, "You'd better use this treatment fast before it no longer works after a controlled trial is done!" A number of substance abuse treatment practice guidelines have been developed concerning delivery of cost-effective care; client outcomes after addictions treatment; management of alcoholics in private practice; guidelines for patient-treatment matching; treatment of patients with psychosis; physical and sexual abuse related trauma; withdrawal symptoms; alcoholic ketoacidosis; seizures: secondary anxiety disorders and depression; prescription drug abuse; neurologic complications of alcoholism, and chemical dependence guidelines. Even though most of these are rather narrowly focused and not fully operationalized, they have in many cases been the first attempts to formalize treatment procedures. Recent developments are more broadly based (*e.g.* American Psychiatric Association; American Society of Addiction Medicine; American Psychological Association; American Nurses Association; National Association of Social Workers; The Centre for Substance Abuse Treatment [TIPS]). The development of practice guidelines in the addictions is proceeding swiftly, despite an absence of data regarding the processes by which guidelines can most effectively be developed, disseminated and evaluated (Walker *et al.,* 1995). There is definitely an opportunity for evidenced-based evaluation of practice guidelines!

I would like to conclude with a description of an initiative being taken far outside the drug abuse field which we might embrace and that might serve our field and the College well. This initiative is international in scope and is called the Cochrane Collaboration. The basis of this arises from the observations of Archie Cochrane more than 20 years ago (Cochrane, 1972). In 1979 he further wrote, *"It i.v. surely a great criticism of our profession that the have not orgranized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials".* The Cochrane Collaboration is the response to this challenge. The goals of the Collaboration are preparing, maintaining and disseminating systematic reviews of the effects of health care interventions. Though a series of Review Groups, Coordinating Centres and Specially Field Coordinators, the

Collaboration involves individuals worldwide in the objective and comprehensive compilation and evaluation of all randomized controlled trials, the archiving of the evaluations and the preparation of systematic reviews which become available by Internet, CD-ROM and print media.

As I have inferred by bringing the Cochrane Collaboration initiative to your attention, I feel that the College should be taking a lead in the collating, archiving and disseminating of the evidence concerning drug abuse treatment. I do not discount the value of various reviews and practice guidelines that have been, or will be, compiled. However, an initiative which is strictly evidenced-based and contined to randomized controlled trials will do much to make unbiased information available and to identify in an objective way what research is needed. The College should be a vocal advocate for evidenced-bad treatment and prevention, and promote research which will provide the information needed for the health of the public. Our annual scientific meeting is an impressive display of individual research projects. In my view, it should also be the time in which the College demonstrates leadership in the presentations that are broad based and have international impact. In essence, I believe the College can lake the lead while working with others by placing a much stronger reliance on evidenced-based treatment and prevention as reflected in randomized controlled trials; in assembling publicly available analyses of existing data; and identifying areas where research can yield evidence which will have practical and scientific importance. Other fields have effectively managed to approach questions of public health importance on a far larger scale than our field typically has been able to (*e.g.* cardiovascular disease, oncology, nutrition).

As President of the College for the past year, I have had the opportunity to become involved in numerous meetings on behalf of the College. Among these was an interesting Constituents meeting organized by Dr. Alan Leshner at which members of NIDA's constituencies came together. The College was pleased to be included. At the meeting more than 30 different groups were represented--most of them with an orientation to direct treatment and not members of a research world. The discussions were interesting and thoughtful and as you might imagine covered a very wide range of perspectives. It was a challenge to try to think of practical ways that the College could build on the voiced desire of those present for more effective liaison and collaboration. It is readily apparent that there is a great willingness for collaborative initiatives among participants in the treatment and research arenas. To this end, for the Plenary Session I have invited Mr. David Mactas, Director of the Center for Substance Abuse Treatment, and Dr. Alan Leshner, Director of the National Institute on Drug Abuse, to join me. I am delighted they have agreed to be here. The College has had a long standing interest in treatment research and the interface of basic research with treatment.

I hope they will agree with me that evidenced-based treatment and prevention are not only a shield in the present times, but also a sword if we will wield the sword effectively.

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PLENARY SESSION PRESENTATION

D. J. Mactas

Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, Department of Health and Human Services, Rockville, MD

It really is a pleasure to have been invited to speak before you. I was reminiscing with the Board last night that, although I've known of the College for some time, my exposure was at a previous meeting. I was attending a meeting at the College and I was standing outside the ballroom listening to presentations because I didn't have a name badge. Once again, I haven't gotten my badge. But knowing so many of you and having interacted with you for so long, this is really terrific to be here.

CSAT Collaboration

The Center for Substance Abuse Treatment resides at the Substance Abuse and Mental Health Services Administration, which resides in the Public Health Service, which resides in the Department of Health and Human Services.

CSAT, and its colleague agencies, the Center for Mental Health Services and the Center for Substance Abuse Prevention operate under the SAMHSA umbrella. CSAT has a budget of approximately $1.4 billion, of which $1.2 billion is block grants. The block grant is a congressionally determined formula for distributing funds to the states and territories so that they can distribute dollars in accordance with their substance abuse treatment and prevention needs.

The remaining budget at CSAT is comprised of demonstration and training awards. The SAMHSA portfolio of demonstration programs is approximately $566 million. As I explained to the Board last night, the projection for 1998 is that the portfolio will be diminished by $300 million--which will move from demonstrations into service.

Demonstration programs are designed ostensibly to answer very significant questions in order that we who execute knowledge and discovery and revelation can shape the field to some extent. The view has been that much of those resources have been applied toward service delivery and not to learning. Thus, there has been a diminution in overall demonstration portfolios. It's a critical issue which I'll revisit in a minute.

So, toward organizational integration, CSAT works closely, but not closely enough, with its colleague agencies and also with the Institutes, NIAAA and NIDA specifically.

You may have heard there is a new Congress. This is a very, very interesting challenge to all the government, especially folks who came down at the time the Congress turnied over. Had I to do it over again, I would do the same thing, but I would prepare myself il little better.

To assuage "the slings and allows" that occur naturally from a new job and a new Congress. I take great comfort in having found a very good friend and colleague in Dr. Ahan Leshner, the Director of NIDA, with whom I and CSAT work very closely. And we are constantly challenged by how much we can do together to complement each other's efforts. We are doing so many good things separately, and we can do so many good things together, and we have started to pursue that in earnest.

In addition, CSAT works very closely with the Department of Justice, and other Federal entities.

Evolution/Isolation

The Institute for Health Policy Studies, under its then Director, Dr. Philip Lee, who is now the Assistant Secretary for Health, published a paper a number of years ago that looked at the state-of-the-art in substance abuse treatment and concluded that the field of substance abuse treatment was one that had evolved in isolation.

Perhaps that's a strong statement. but there are elements of truth there if one is to measure isolation by the degree to which integration. incorporation and cooperation are achieved or not achieved.

It's always been my belief that we have in fact evolved in isolation. To a great extent that occurred because we treat people who are largely isolated. I find that kind of isolation endemic to the field of substance abuse treatment.

The notion of evolution in isolation is an interesting one at this point in time. This is a very critical time for this field. I don't think we have the luxury of evolution at this point, if the field is going to not only survive but develop along some planned course. So what the Congress cried out for is not evolution to be sure, but genetic engineering. Those of us who constitute leadership, those of us in this room, need to take things in our own hands and shape them, shape not only content, but shape what needs to be learned. We must take what needs to be learned and shape the field of service delivery, and also recognize that we need to do something to further the field itself.

Stigma and the Substance Abuse Field

CSAT has been principally involved for a very long time in providing access to quality care for the high percentage of folks who rely on government subsidy for health cure and delivery of services. However, there is an anvil of stigma that keeps the field down to a great extent.

I was intrigued by a survey that was done on the general public and people in this field about their view of this disease. Given the negative stereotype of the substance abuser, CSAT might be viewed as the Center for the treatment of those of moral weakness. This is stigma. To the general public, there is a fusion between the view of those who are in the throes of substance abuse and those who work with those in the throes of substance abuse.

The view of moral weakness here is pervasive. It is just very compelling to see this quantified in the survey. Lest you believe that if you provide services to the stigmatized population, that the stigma only applies to the client and not you, I would submit lo you that this is folly. And if you feel that that's not the case, I would ask if you have experienced what I have experienced with my mom.

I have been in my mom's house in Florida when she is trying to describe to her friends what I do for a living. I love my mom. And it hurts me to see her agonize over describing what her son has done 30 years. I would hope that some of you have experienced the same. Try to generalize what you do for a living. It really doesn't fit into the common lexicon or parlance of humanity. It is kind of apart from, and not part of, the rhyme and rhythm of life.

Unless we can make some significant impact on the public's opinion of the substance abuser, there isn't much hope for the rest of us.

The fusion goes all the way up. Those folks are stigmatized. They were stigmatized before they put a needle in their arm to be sure, many of them based on where they are coming from. Then they put a needle in their arm, snorted, or skin popped, or ingested or whatever they did. Then the stigma becomes heightened. For those who treat those folks -- it's guilt by association.

If you are in the chain working with folks who rely on the government subsidy, if you treat them, you are stigmatized. If you fund the treatment programs, the civil and state authorities are stigmatized. If the Federal government funds a single state authority, you are stigmatized. You can't draw the line very clearly anywhere. It just goes all the way up unless we can start to make some impact.

Research and the Natural Laboratory

One of the enterprises that I think provides a formidable challenge for us is the notion of incorporating research into the way we do business...certainly by looking at the network of community-based providers. I have a special interest in that I was involved in substance abuse treatment at the community level for so long. To a great extent, these organizations were this nation's response to spiralling health care costs, coupled with the refusal and ineffectiveness of other interventions to deal with these groups of people they gave rise to the emergence of the community based system.

One of the programs that I operated before I came to CSAT was a residential therapeutic community in New England, staffed 24 hours a day, providing therapy, education, remediation, vocational rehabilitation, food, clothing, shelter, family therapy. What we got the state to provide was $26 a day. You want to talk to me about cost containment'? All of those community-based organizations that evolved at the same time were funded with Federal dollars that had nothing lo do with actual expenses. You should talk to these programs about cost containment in the new, emerging environment of managed care.

It is interesting what has happened. Given the fact that heallh care costs have spiralled, which they have, it's interesting that a broad contingent of well-run agencies who were not present for the "crime" have been invited to the sentencing. They are involved now in the prescription as to how we can contain these spiralling costs.

So I am an advocate, and a passionate one, for the community-based system. But one of the crises that faces the community-based system of providers is that the folks who run or the folks who tend to run these organizations, are people who are career counselors.

Whenever I speak before a large group, I ask: "Of those of you who operate community-based organizations, how many of you would say you are, by profession, a researcher?" Few hands go up.

Research is viewed too often as an elective in the operation of a treatment organization. It is not elective. It is part and parcel. As a matter of fact, you cannot do treatment unless you have the capacity to not only ask questions, but to answer them. Apparently, researchers aspire to knowledge, to learn more. And counselors aspired to mobility. I don't know how we got into this position. But the people who run programs tend to be people who were counselors that moved their way up the ranks. Researchers don't take over the programs. We have to enhance the capacity of programs to conduct research.

One of the most glamorous things that has happened to me in my carreer is when I spoke before your council, Dr. Leshner. You said you didn't know whether to introduce me as a treatment provider or a researcher. That was very flattering to me. I think if you want to be a good treatment provider, you have to be a researcher.

And what is a researcher? It is somebody who asks good questions, is committed to finding out the answer, and committed to applying that which has been learned. We need to change the environment so that learning shapes practice.

Those who would be the most outspoken proponents of the research and demonstration agenda that has been executed over the years would concede that if we ask to what extent have we shaped the services in light of what we have learned, the answer is: not enough. Yes, there are the NIDA Monographs and CSAT Treatment Improvement Protocols--but too often these are documents that die on shelves.

We need to have a commitment to giving life to that which has been learned. And the natural laboratories, the demonstration programs that we operate at CSAT--where there is a diminished portfolio of monetary support--speak to the potential of natural laboratories.

We have a challenge to apply what we have learned and participate in that which is going on at NIDA to improve community-based treatment efforts. We are in the research business and we are in the demonstration business.

The Center for Substance Abuse Treatment and David Mactas are very excited to have been engaged by the College. My predecessor was very creative to get involved. Having spent some time during the breakout sessions, I thought, "My!, what a group of scholars!" My perception hasn't changed. I hope that someday we'll get to know each other better and know each other on a first name basis.

I look forward to speaking before you again. And, I hope the next time that I speak before you we will be able to look back at a time when the anvil of social stigma was keeping the field down, and can look at the progress that we have made. In addition, I hope we can look at the integration not only of systems, but of the notion of implementing research demonstration into treatment practice. I look forward to that day very much, as well as a continued friendship with so many of you.

Thank you very much.

DRUG ABUSE AND ADDICTION RESEARCH: OPPORTUNITIES FOR PROGRESS IN 1996

A. I. Leshner

National Institute on Drug Abuse, National Institutes of Health, Rockville, MD

I am very happy to be here again this year representing the National Institute on Drug Abuse (NIDA) as Director, and to have the opportunity to update all of you on some of the significant progress we have been making in shaping our research agenda to best meet the needs of the field. I also want to apprise you of some issues that are having or potentially may have a major impact on the field.

In my role as NIDA's Director, I cannot help but feel an enormous sense of pride in coming to the annual CPDD meeting--as I know many other NIDA staff do-pride in our ability to enable a phenomena1 amount of stellar research which virtually crosses the entire breadth of the CPDD program. Each of you conducting the research are playing a vita.! role in advancing the field of drug abuse and addiction and in ensuring that NIDA's research programs continue to flourish.

I would like to remind you that this year marks the 60th anniversary of NIDA's Addiction Research Center (ARC) and we have scheduled a number of celebratory events which will be taking place over the course of this meeting, beginning with a scientific symposium. Established in 1935 as a Narcotics Farm whose primary role was to study opiate addicts, the ARC, over time, has evo!ved into one of those wonderful jewels when: every aspect of drug abuse and addiction has been studied and where many of the field's most notable discoveries originated. I invite all of you to attend what promises to be an outstanding program this afternoon.

REORGANIZATION

During the past year, NIDA has undergone a restructuring of its extramural branches which has helped in refocusing and refining some of our research programs and in expanding our activities in areas of growing importance to the field. We have created a new Behavioral Sciences Research Branch, headed by Dr. Jaylan Turkkan, through which we intend to dramatically broaden our basic behavioral research portfolio. While still maintaining the current research base NIDA has traditionally supported, this newly established branch will be attempting to stimulate research on related behavioral processes and aspects of drug abuse such as cognition and perception, motivation, and social factors. We will also be encouraging the exploration of new and novel approaches, models, and paradigms for studying drug abuse and addiction as well as behavior change models relating to HIV/AIDS.

I am delighted to report that the staff of our new Behavioral Sciences Research Branch will be holding a roundtable discussion as part of the CPDD meeting to provide an opportunity to discuss some of the work that is currently underway and emerging areas of emphasis.

Another major result of NIDA's reorganization was the creation of a new Etiology and Clinical Neurobiology Branch within our Division of Clinical and Services Research (DCSR). This branch, which is led by Dr. Joseph Frascella, was established in an attempt to infuse nueroscience into our clinical research portfolio in a far more prevalent and prominent way. Here, we would like to support more research on the human brain which is conducted in clinical settings, taking advantage of the opportunities offered by new clinical research tools, including a variety of imaging technologies.

The work we intend to support through this branch will complement ongoing studies being funded by our two basic neurobiology research branches within the Division of Basic Research and the extensive neuroscience research being conducted at NIDA's Division of Intramural Research at the Addiction Research Center. Staff of the new branch will be encouraging research on the development of new or refinement of existing biological

and neurological assessments that will help to elucidate risk and protective factors for drug dependence. We would also like to support work which employs new technologies such as imaging to assess the level of effectiveness of different types of pharmacological and behavioral treatments.

The Institute reorganization has also helped to strengthen NIDA's leadership in the area of AIDS. Headed by Dr. Harry Haverkos, the staff size of NIDA's Office on AIDS has been significantly expanded during the past year and their work has helped to coordinate, define and expand our research programs in this area. As evidenced by the satellite conference to this CPDD meeting which we sponsored on June 9-10 on "Drug Abuse and Aids", we are becoming increasingly pro-active in our attempts to identify knowledge gaps and to set a research agenda for drug abuse related HIV transmission and AIDS.

GRANT REVIEW

Over the past year an area of great concern to most of us has been grant review and what will happen when, ultimately, this function is merged with that of NIH. Although discussions on this topic with key individuals within the NIH system have generally been struggles against rigidity and conservatism, we have actually met with a lot of success. Basically, what we have received agreement to is that when the ultimate structure of the Division of Research Grants (DRG) is determined that, rather than "shoehorning" our proposals into existing committees, our proposals will be joined with any other with which there may be overlap and then new committees will be created. This is an extremely important issue. The fact is that every review committee that currently exists has a culture, including our own. If we were to simply add several drug abuse researchers to an existing committee it would not change or influence the existing culture to any measurable degree. What we want is for totally new committees to be created that will meet the needs of our field. And we now have agreement from the necessary key NIH staff to ensure that this will be the case.

At the same time, the Division of Research Grants (DRG) into which your proposals will be is also undergoing tremendous change. The retirement of DRG Director, Dr. Jerry Green, provided the impetus for NIH Director, Dr. Harold Varmus, to take a very fundamenta1 look at peer review at NIH. I was fortunate to be on the committee that was involved in this work which basically focused on two areas. One area is the question of how you decide what is reviewed at DRG versus what is reviewed within a separate Institute. Areas that are truly multiple institute, for example very basic research phenomena such as molecular neurobiology, will most likely be reviewed in DRG. However, as the nature of the research gets more mission related, for example, clinical treatment research, it will be reviewed at the individual institute level. The specifies of this issue have not yet been finely worked out but agreement has been reached on the fundamental principle. From our point of view, this is a phenomenally important advance.

The second issue of concern is related to the review of proposals in new areas of science. This is an issue that not only affects NIDA review but also impacts NIH review broadly. The basic question involves how to review proposals in hand, but, at the same time, be preparing for emerging areas of science. The NIH DRG committee spent a tremendous amount of time dealing with this issue, deciding that the solution should involve having much broader review committees in the future. In my view, this will be a tremendous advantage for researchers in our field

We at NIDA, have also recently finished revamping our own review structure, establishing discreet committees in each of our key priority areas in preparation for the ultimate integration with the NIH review systems. So we have made enormous progress in the last year around the whole issue of grant review.

REFINING NIDA'S RESEARCH AGENDA

NIDA has been involved in a great many activities over the last year which have been helping us to shape our research agenda. We have had 11 or 12 major consultation meetings with experts in various areas relating to

drug abuse and addiction. These meetings have proven lo be extremely productive in terms of identifying emerging areas and generating recomendations for future research. We also convened a meeting of representatives from about 40 of NIDA's major constituency groups, including CPDD, to solicit their input on ways we can make our research more relevant and useful to the field. In response to needs articulated by participants at this meeting, we have set up a number of mechanisms to help disseminate information about our research findings more rapidly than we have in the past and to a far broader audience. The interchange this meeting has brought about has proven to be so valuable and the follow up activities such an enormous success that we have decided to have a second meeting of this type in thc fall.

New Initiatives/Program Announcements

NIDA has issued a number of new program announcements this year and expects to release additional ones in the near future. From my perspective, this is a very positive indication that the work that has been done in the drug abuse field has provided a superb base for moving into the next decade.

AIDS

The issues of AIDS and drug abuse have become totally interwined. There no longer seems to be a clear separation between the two. We, as an institute, are acknowledging this complex interrelationship in far more explicit ways than we ever have in the past. This year we issued program announcements with the goal of stimulating research on AIDS, drug abuse and neurobiology; HIV disease progression in drug users; and HIV risk behaviors, determinants, and consequences. We have also joined with the National Institute of Mental Health (NIMH) in issuing an aunouncemcnt to encourage research on prevention of relapse to high risk behaviors and with NIMH, the National Institute on Alcohol Abuse and Alcoholism (NIAAA); and the National Institute on Aging (NIA); an announcement to support research on family interventions and HIV/AIDS.

Neuroscience

As I mentioned previously, we have been trying to infuse neuroscience throughout our research programs using a variety of different mechanisms. In addition to creating a new branch within DCSR, we have also released a program announcement to support human basic and clinical neuroscience research on drug addiction. Other area in which we have increased focus include neurosciencc research of nicotine and nicotine abuse; and neuroscience networks in basic drug abuse research.

Treatment

Through a variety of initiatives, NIDA is continuing the evolution of its treatment program. As you know, Drs. Jack Blaine and Lisa Onken have been working on the behavioral therapies development programs for some time now and have been quite successful. In addition, we are trying to get involved in work relating to linkages with primary care, and to the treatment of individuals with co-morbid mental and drug abuse disorders. Also, our Medications Development Division is attempting to find novel human and animal models that will help move us forward in the whole medications development arena.

Health Services Research

During the past year, we have been engaging in increased efforts to expand our health services research portfolio. We published program announcements designed to stimulate the establishment of health services research centers as well as drug abuse health services research and HIV/AIDS.

Epidemiology

Our epidemiology research programs has also grown during the past year. Two areas we have targeted for expansion are drug and alcohol use and abuse in rural America; and local population/area epidemiologic research on drug abuse correlates and consequences.

NIDA Workgroup

The internal NIDA workgroups we have established around our key priority areas have been extremely successful in augmenting the progress being made in our program divisions. The workgroups have identified emerging areas in need of attention and emphasis, devised many innovative mechanisms to advance the field in their particular area, and allowed a great deal more interaction among Institute staff.

EMERGING POLICY ISSUES

In addition to new opportunities and programmatic changes going on at NIDA, there are also a number of emerging policy issues of which I would like to make you aware. The first is the emergence of an AIDS testing and counseling policy which was developed with the help of our National Advisory Council on Drug Abuse. NIDA's AIDS counseling and testing policy basically. says that researchers funded by NIDA who are conducting research in community outreach settings, clinics, hospital settings, or clinical laboratories and have ongoing contact with clients at risk for HIV infection, are strongly encouraged to provide HIV risk reduction education and counseling and to offer HIV testing. NIDA will help to defray the cost of implementing this policy for people who have existing grants. It is my understanding that virtually every researcher who does clinical research in our field is already doing this anyway. But we felt it was important as a public health statement to explicitly articulate this policy.

The second policy issue I would like to alert you to is that NIDA will soon have a document outlining its guidelines for research centers. As with our AIDS Counseling and Testing Policy, the National Advisory Council on Drug Abuse has been working very hard in helping us define our position on this issue. Although in the past NIDA has supported primarily only the P50 Centers mechanism, in the future we will begin to make better use of the full range of centers' mechanisms available in an effort to ensure that our research center program is best accomplishing its intended purpose.

The last topic I want to address is one on which we at NIDA need your help. The one thing I have been most struck about since coming to NIDA is what I have been calling the "unique disconnect". That is, there is a tremendous disconnect in this country between the scientific facts and what the public perceives as the true nature of drug abuse and addiction. The truth is that if we are going to make any real progress in battling the most serious and pervasive problems facing this country, virtually all of which are tied to drug abuse and addiction; and if we are to advance the cause of those people who are addicted to drugs, we are going to have to do far more pro-active things to bridge that disconnect between perception and reality. And all of you are actually the essence of the way in which we will be able to achieve this goal.

Although all of us here in this room know about the splendid advances that have been made in this field, we are the only ones who know the secret. Increasing the awareness of the public and even the practitioner and advocacy communities will be a difficult uphill battle and one in which we will have to work together. This is the primary reason we have begun the process of interacting so much more actively with constitutency groups. It is also a part of our collaboration with CSAT and CSAP. And it is part of our working with other agencies to make clear that we have the scientific base to change the way in which drug abuse treatment, prevention, and policy are addressed in this country.

Within the NIH, every Institute Director is asked, over the course of his or her fist year, to articulate the goals he or she would like to accomplish during their tenure. And so I have declared NIDA's goal for the year 2000.

I would like it to be that, in the United States of America, science has replaced ideology as the foundatoin for drug abuse prevention, treatment, and policy. And the College on Problems of Drug Dependence right now is the single core element that we have in that effort. The scientific research that you are engaged in is superb. We need more of it, and we need to advance, but no matter how stellar our work, it will not do us much good if we keep doing it in secret. NIDA is totally committed to doing all that we can to bridge the "disconnect". But we all are going to hove to engage in far broader research and knowledge dissemination activities so that we can change public opinion and bring a broader understanding. Until we do this, we will continue to be severely hampered in our efforts to remove the stigma or to solve the drug abuse and addiction problem in this country.

Alan I. Leshner, Ph.D.
Director
National Institute on Drug Abuse
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PRESENTATION OF 1995 J. MICHAEL MORRISON AWARD

C. P. O'Brien

University of Pennsylvania, Treatment Research Center, Philadelphia, PA

Michael Morrison was an outstanding Executive Secretary at NIDA during the 1970s. After Mike's death at an early age, the College on Problems of Drug Dependence decided to set up an award to honor dedicated public servants who typified Michael Morrison's example of hard work and concern for advancing science in the field of substance abuse. Our honoree this year has a long history of service, at NIDA and at other agencies.

Jack Blaine, M.D., is a psychiatrist who has made numerous contributions to the drug abuse field over the past 20 years as a research administrator and clinical researcher at NIDA and NIMH. His work dates back to the 1960's where he was instrumental in developing the research program on the medical and psychological effects of marijuana in humans, and in writing the section on the effects of marijuana in man for the first *Marijuana and Health Report* to Congress. He was also instrumental in developing the report of the National Commission on Marijuana and Drug Abuse where he was Assistant Director for Medical Sciences.

Jack began working for NIDA shortly after its creation in the early 1970s. He was one of the leaders of the LAAM Development Program that involved organizing a multi-site study of over 5,000 heroin addicts. He wrote several important papers describing these studies.

In the late 1970's, Jack was the driving force behind a program to study the effects of psychotherapy in substance abuse. This was the first scientific approach to the question of whether psychotherapy is effective in substance use disorders. As a result of his work, several contracts were let and important studies were conducted. He was co-author of one of these studies which was published in the *Archives of General Psychiatry.* This work has had an important influence on the field.

In the early 1980's, Jack returned to NIMH where he directed studies on electro-convulsive therapy. This led to the development of standards for the safe and effective use of ECT. In 1986, he returned to NIDA where he became Chief of the Treatment Research Branch. Under his leadership the research in this branch has grown from about $6 million to over $100 million. He helped to establish the NIDA Medications Development Program and the NIDA Treatment Research Units.

Jack Blaine is a creative thinker and dedicated public servant who has a clear understanding of important research issues in the field of substance abuse. In addition to the work that he has actually published, he has stimulated and coordinated far more research that does not bear his name. Because of his many contributions to the field, Jack Blaine continues in the tradition of Michael Morrison. He clearly merits the award for outstanding government service.

INTRODUCTION TO THE NATHAN B. EDDY MEMORIAL AWARD RECIPIENT

T. R. KOSTEN

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New Haven, Connecticut

I take great pleasure in introducing Herbert D. Kleber as the Nathan B. Eddy Awardee of the College on Problems of Drug Dependence. The focus of Dr. Kleber's professional career has been on understanding why individuals use and/or abuse certain psychoactive drugs and on how to improve treatment methods when they try to stop such use. His efforts have led him to apply knowledge from the laboratory to bridge the gap between the understanding of laboratory and epidemiologic findings to that of individual behavior and the role of the community and government.

Dr. Kleber's interest in drug abuse began during residency when he studied hallucinogenic drug use on the Yale Campus. Such use had just begun there and during residency he carried out both clinical studies who developed adverse effects to these drugs as well as survey of such drug use on campus. The latter provided an objective index of the extent of such use, countering some of the hysteria, while the former was one of the first studies of possible prolonged adverse effects that could arise from unsupervised use of hallucinogenic drugs. Following residency at Yale, Dr. Kleber spent two years at the U. S. Public Health Service Hospital in Lexington, KY, then the leading center for addiction treatment and research. Upon his return to Yale as a faculty member in 1966, he became involved with local efforts to do something about the problem of addiction in New Haven, culminating in a grant from NIMH in 1968 that led to the formation of the Drug Dependence Unit.

Dr. Kleber's endeavors have included developing new treatment methods and improving upon existing ones; advancing psychiatric knowledge about individuals who become drug abusers; evaluating various preventive efforts, such as drug education; and finally, developing investigators who have become important contributors to the field. In the 1970s, Dr. Kleber also contributed to public knowledge through being on the first National Advisory Council to the NationaI Institute on Drug Abuse from 1975 to 1979, chairing the Mayor's Drug Task Force in New Haven, and being on the Connecticut Governor's Drug Advisory Council.

From 1968 to 1982, Dr. Kleber's treatment research endeavors were concentrated in four principal areas narcotic antagonists, methadone maintenance, narcotic detoxification, and multi-modality approaches to treatment. He began a methadone maintenance program in 1968, one of the earliest such units in the country. The New Haven methadone program difffered from most other units in the country in insisting on a high level of psychosocial rehabilitative efforts and in involving patients with clinic governance. In the early 1970s, when most methadone programs believed that individuals could not be detoxified successfully from methadone, Dr. Kleber and colleagues began a detoxification program and with follow-up studies, demonstrated that it was possible for many patients to do so.

Since many patients, however, remain on methadone for long periods of time, he was concerned about the long-term safety of methadone and developed a series of studies in collaboration with leading faculty at Yale Medical School to look at the effect of methadone on various organ systems. The integrated, multi-modality and research approach to the treatment of the drug-dependent individual led to the unit in 1975 receiving the Gold Achievement Award of the American Psychriatric Association for its treatment, research, prevention, and community endeavors. He was also promoted to Professor of Psychiatry at Yale.

The problem of narcotic detoxifications, a long-standing concern of Dr. Kleber, led to his collaboration with Drs. Aghajanian, Gold and Redmond in the development of clonidine as a detoxification agent for narcotic withdrawal based on its effects on the locus coereleus. Dr. Kleber and colleagues also developed an ultra-rapid method of withdrawal, combining the narcotic suppressing effect of clonidine with the withdrawal precipitating effect of naltrexone. This ultra-rapid withdrawal method has been shown in recent studies from the Yale group

to have a success rate as high as 90% in outpatient programs. For his work with clonidine, Dr. Kleber was a co-recipient in 1981 with Drs. Aghajanian, Gold and Redmond of the Foundations' Fund Prize for Psychiatric Research given by the American Psychiatric Association.

During the latter part of the 1970s, Dr. Kleber became interested in the area of psychological research in addiction, specifically the relationship of psychopathology and drug abuse. These studies were done in collaboration with Dr. Myrna Weissman and under Dr. Bruce Rounsaville's leadership.

By the early 1980s, cocaine abuse was becoming a major public health problem in New Haven as well as the rest of the country. He and Dr. Frank Gawin, who had completed his psychiatric residency at Yale and joined the Substance Abuse Treatment Unit, tried first lithium, then methylphenidate, and finally desipramine for treating cocaine addiction which remains the best studied medication for the treatment of cocaine addiction.

I begun my work with Dr. Kleber during my residency and stayed on after a Robert Wood Johnson fellowship to collaborate both in the cocaine studies and in studies improving opiate detoxification, especially with buprenorphine. I have enjoyed working with him as a mentor, colleague, and friend.

During the decade of the 1980s, Dr. Kleber received numerous awards for his contributions. These included the Nyswander-Dole Award for outstanding contributions to methadone maintenance treatment (1986), the Founder Award for distinguished contributions in research, teaching and clinical work in the substance dependence field from the American Academy of Psychiatrists in Alcoholism and Addiction (1987), and the ADAMHA Administrator's Award for Public Service (1986). Individuals trained by Dr. Kleber also have made important contributions in the substance abuse field, including Drs. Rounsaville, Schottenfeld, O'Malley, Carroll and myself at Yale, Gawin at UCLA, Anton at the Medical College of South Carolina, Swift at Brown, and Gold at the University of Florida.

In 1989, Dr. Kleber was asked by William Bennett, Director of the Office of National Drug Control Policy to become the Deputy Director for Demand Reduction at this office. During his tenure as Deputy Director at ONDCP, the funding for treatment and prevention of drug abuse in the United States doubled, and a number of important programs began at his urging.

In November 1991, Dr. Kleber left Washington to become Professor of Psychiatry at Columbia University College of Physicians and Surgeons, and with his collaborator, Dr. Marian Fischman, created a new Division on Substance Abuse at Columbia and the New York State Psychiatric Institute. In addition, Dr. Kleber joined with Joseph A. Califano, Jr., the former Secretary of HEW under President Carter, to found the Center on Addiction and Substance Abuse at Columbia in October 1992. CASA is a policy research center dedicated to advancing awareness of the treemendous cost that American society pays for the problem of substance abuse, and to developing knowledge of effective ways of doing prevention and treatment so as to make these endeavors more acceptable to the public and policy makers.

Recently, Dr. Kleber, at CASA, received a multi-million dollar grant from the Federal Government to study the effectiveness of substance abuse treatment in the United States. He also chairs the Scienlific Advisory Board of DARE, is on two Institute of Medicine committees (one a study of "Needle Exchange", the other "Medication Development"), and is on the Advisory Boards at both Yale and Pennsylvania Research Centers. He is also the co-editor of the recent Textbook of Substance Abuse Treatment, put out by the American Psychiatric Association Press, and the author or co-author of over 180 papers, chapters and books. He is a Fellow of the APA, ACNP, CPDD, and ACP, among others.

In summary, starting from his early days as a resident, Dr. Kleber has been dedicated to learning more about the nature of the problem of drug abuse, improving our methods of prevention and treatment, training individuals who are and will be the next generation of leaders in substance abuse research, and working at a city, state, and national level to inlluence policy development in a way that would be beneficial to the field and helpful to patients. He has made important contributions to understanding and treatment for both heroin and cocaine

dependence, to policy development, and is clearly one of the outstanding individuals in the field of substance abuse, both in the United States and abroad.

THE NATHAN B. EDDY AWARD LECTURE: "A PASSION TO IMPROVE TREATMENT"

H. D. Kleber

Division on Substance Abuse, Columbia University College of Physicians and Surgeons and Center on Addiction and Substance Abuse

Introduction: I am deeply honored lo be this year's recipient of the Nathan B. Eddy Award, perhaps the highest distinction that can be received by a researcher working in the field of drug abuse. Since I never had the privilege of meeting Dr. Eddy, I turned to my Yale historical guru, David Musto, for information about him. David told me about the similarities between what the country is going through now and what Dr. Eddy experienced. Research of all kind was under attack in the 1920s, as it is today. More law enforcement was seen as the answer. By 1927, there were more Harrison Act drug offenders in federal prisons than any other class of offenders, including violators of the Volstead Act. Dr. Eddy feared that policy was occurring without an adequate scientific base. The scarce research dollars had to be used to carry out top quality research. Today we are again faced with drug abuse being a low national priority and an administration and Congress unwilling to defend the importance of drug abuse research, treatment or prevention. Like Dr. Eddy, we must use these scarce dollars to carry out superb research, and then use it to influence policy.

Although during my talk I will be acknowledging my debt of gratitude to many who have been important to me, I should like to single out at the beginning a few of them. My special colleague and partner, Marian Fischman; my children, for their support and wisdom, as well as for their enormous patience all those evenings and weekends when I was working instead of being with them; my wonderful colleagues at Yale, without whom most of the work for which I am being honored could not have occurred; Danny Freedman, who at key times from my residency onward, was there as a mentor and advisor; and finally, NIDA, for the support and encouragement it has given me over the years to make my research possible.

I'm often asked how I got into the whole area of drug abuse. I would like to say it was because of my contacts with drug addicts during my residency, but in fact, I don't recall ever having seen any--only some students in trouble with psychedelics (Kleber 1965, Kleber 1967). It was certainly not because of encouragement from the Yale Department of Psychiatry, which historically has always beeu ambivalent about having drug abuse treatment and research as part of their department; the acting Chair in 1968 even opposed my applying for my initial grant. Nor was it because I was recovering myself: my only addiction has been to nicotine, and fortunately I've been off cigarettes for the last 18 years. No, the real reason I got into drug abuse research was that I trusted my government. I signed up at the beginning of my residency to go into the Public Health Service when I finished, with the understanding that I would then be sent to the Intramural Research Branch of NIMH. Instead, my active duty assignment was to the Public Health Service Hospital at Lexington, Kentucky, which in 1964 was one of only two facilities in the United States devoted to research and treatment of drug addiction. My protests of a mistake fell on deaf ears.

During my years at Lexington, I was fortunate to learn a great deal about addiction, especially from the patients, but also from mentors such as Bill Martin and John Ball. A useful lesson came from George Valliant, a two year wonder like myself, who had difficulty getting permission from the Research Committee to carry out what became his classic ten year follow-up of addicts. George told me, "Herb, if you want to get your research approved, gel on the committee that approves it." That was how George did it, and later at Lexington, when I wanted to do LSD research with addicts and had trouble getting the research approved, that was ultimately how I did it.

After two years at Lexington, I returned to Yale and helped in the opening of the Connecticut Mental Health Center (CMHC). But having been at Lexington, I was a marked man: addicts sought me out for treatment, parent groups asked me to speak about adolescent drug use, and physicians kept calling me for advice. Finally, I decided that a career in addiction research was inevitable. With the help of my late friend and mentor, Gerry

Klerman, then heading the CMHC, I wrote my first grant application to NIMH, received it in 1968, and we became one of six centers in the United States set up to do treatment and research in drug abuse. Along with the center that Jerry Jaffe established in Chicago, the Yale Drug Dependence Unit (DDU)--now called the Substance Abuse Treatment Unit (SATU)--is one of the oldest and probably only still continiuously operating true multi-modality treatment and research center for drug abuse in the United States. Unfortunately during these three decades, there has been no shortage of addicts. The number trying illicit drugs has risen from less than 4 million in 1962 to almost 80 million in 1992, and the number of addicts has risen proportionately, from about 300,000 to about 6 million.

Most of the research work we carried out at Yale during those years arose from clinical problems that we were not able to adequately solve. Listening to patients and clinical staff is often the best guide, both to what needs to be done and possible solutions. I was reminded of this when the FDA, in December 1994, approved naltrexone for the treatment of alcoholism--the first agent for alcoholism in 41 years. Izola Hogan, the DDU nurse at Yale who has been giving naltrexone since we first began using it in 1973, remarked that this use could have been discovered a lot earlier, that she had been noting for the last 15 years that patients on naltrexone seemed to drink less than before they had started. Since I knew from my "book learning" that a narcotic antagonist could not block the reinforcing effects of alcohol, I attributed her clinical observation to patient selection. We're often not as smart as we think we are! An important corollary is that if you want to do good clinical research, it's a major advantage to be running good clinical programs. The substance abuse treatment program at Yale and the APT Foundation is, I still believe, the major clinical research unit in the United States due to the ability, dedication and experience of the staff, most of the lop clinical staff having been there since the late 1960s and '70s, and to the constant infusion of the clinical work with the research ethos of never being satisfied and continuing to try new things.

The guiding theme of my work since 1968 has been how to improve treatment of addicts through research. The treatment research has been focused on six areas: 1) developing a true multi-modality treatment system; 2) improving methadone maintenance; 3) use of narcotic antagonists; 4) improving narcotic withdrawal; 5) developing new methods to treat cocaine dependence; and 6) studying the role of psychopathology in treatment outcome. Offshoots of these have included advancing psychiatric knowledge about individuals who become drug abusers; evaluating various prevention efforts, such as drug education; developing investigators who will become the important contributors to the field; and informing public policy at the local, state, and federal level with accurate scientific knowledge. My earliest contribution to public knowledge was through a daily radio spot for live years in the early 1970s on 35 radio stations throughout the country: "Turn On to Drug Facts with Dr. Herbert Kleber". I also had the good fortune to be on the first national advisory council to NIDA, from 1975 to 1979, the one which recommended moving the ARC from Lexington, where research was no longer possible because of new regulations regarding prisoners. to its current site in Baltimore.

A Multimodality Treatment System: The initial modalities of the Drug Dependence Unit were a Central Evaluation Unit, a Methadone Maintenance Program, an adult residential therapeutic community modeled after Daytop Village in New York, an outpatient drug-free program primarily for adolescents, and a community outreach storefront called NARCO. The research focus beginning in 1968 flowed out of the need to improve these programs, to develop new ones, and, ultimately, to have a comprehensive multimodality approach to treatment (Kinsella, *et. al.,* 1974; Kleber 1974).

In 1969, the first progmm we added was a day program for adolescents, Veritras, when it became clear the outpatient approach was not sufficiently intensive. We added use of narcotic antagonists to the day program, first oral naloxone, then cyclazocine. When day treatment proved insufficient, we opened an adolescent therapeutic community, Alpha House, in 1970, and then an accredited therapeutic school for adolescents, COPE, in order that the adolescents would not fall behind in their academic work and to use the therapeutic insights to improve academic performance as well. A central vocational unit to provide vocational training, the first such unit in the country affiliated with a drug program to be accredited by the national accrediting body, CARF, was begun in the mid-1970s, as we relearned the old truth that it's had to rehabilitate an addict who has nothing gainful to occupy him. After numerous frustrating battles with existing hospital clinics to get adequate medical

and prenatal care for the addicts in our various programs, we opened our own Central Medical Unit to provide medical care to individuals in any of our units. Our patients had problems with alcohol as well as illicit drugs, and the lack of adequate alcohol treatment in the community led in the mid-1970s to opening the Alcoholism Treatment Unit, and a name change from the Drug Dependence Unit to the Substance Abuse Treatment Unit. Likewise in the early 1980s, the emergence of cocaine led to development of a cocaine treatment program and crack's devastating effect on pregnant women led in the late 1980s to opening a special program for pregnant addicts. What made it possible to add all of these treatment modalities was that, in 1970, we began our own foundation, the APT Foundation. APT with its dedicated community board tied us more closely to the needs of the New Haven area and provided the flexibility to more readily obtain funds for treatment expansion. By the time I left Yale in 1989, there were about a thousand patients in treatment for substance abuse at any one time, of whom about 80% came under the auspices of the APT Foundation, and millions in research funds, much of which was under the APT Foundation.

The creation of a treatment unit that delivered the highest quality treatment available while being supportive and friendly to research was a tribute to Charlie Riordan, who from the early 1970s to the mid-1980s was the Clinical Director of SATU and responsible for all the programs. His role in keeping the treatment programs running at such a superb level was taken on in the mid-1980s by Rich Schottenfeld, now the overall SATU director who carries out an organized and effective program at a time of major budget constraints. Neither the clinical nor research expansion would have happened without Roz Liss, who joined me as administrator in 1968 and is still the administrator of APT and SATU today. Roz worked 16 hours a day, believed the rest of us should do likewise, and always felt that we weren't doing enough because too many addicts were still not being adequately treated. Roz would come up with more projects in a week than most of us would in a year, and my main job became restricting us to only adopting 10 to 20 percent of them, which still kept us working at 150%. and getting more grants and carrying out more treatment expansion than any of the rest of us would have attempted. The clinical and research expansion occurred without a dilution in quality, a tribute to a group of seven clinicians who worked with me for over 20 years, and are all still at Yale keeping the programs running effectively. Gerry Bryant and her husband, Ray Bryant, are graduates of the methadone program and now run the two major methadone programs. When they came to us, they did not have high school degrees; they went on to get their high school degrees, their college degrees, and Gerry went on to a masters degree as well. I will always be grateful for the insights that the Bryants have given me into the inner-city addict, as well as their skills in running the programs. Vinny Nuzzo and Carl Calabrese are both graduates of our Daytop program. Vinny has been running Daytop for many years, and Carl has been a key therapist in the outpatient treatment programs. They are both tender and tough, and know how to support addicts while demanding the best from them. Izola Hogan and Barbara Clinton are both nurses. Izola was the nurse who first began the naltrexone program with us in the early 1970s and was critical to the early work with clonidine as well. Naltrexone can be a difficult drug to keep patients on. Izola provides the knowledge, the empathy, and therapeutic skill to help them. Barbara Clinton has been a nurse in methadone practically since our program opened. She is a large woman, with enough nurturing and love for staff and patients. She can be tough but caring, and without her regular hugs, a day would not have seemed complete. Finally, Patrick O'Connor, the only M.D. in the group, made our central medical unit into the premiere such program in the country. The eighth person would be David Musto, the preeminent historian. Although he doesn't think of himself as a clinician, he was actually the first director of our upscale Park Institute methadone program, and has remained a sage advisor and policy guru to the senior staff of SATU.

The diversity of programs developed in New Haven stems from my strong belief that there is no one treatment for addictions (Kleber 1989). Addicts are a heterogeneous group and, not only are different treatments needed, but the same addict may need a very different approach at a different stage in his or her addiction cycle. The vital elements are the appropriate assessment, being able to move patients to different programs, and not simply assuming that failure is the patient's fault. While that may be the case, it is also true that patients may do better in different modalities. And a patient who may seem unmotivated in one program, can get motivated in another. Intensive outpatient programs have been especially underrated as to effectiveness. As I said on other occasions, anyone who tells you they have <u>the</u> treatment for addiction is lying, either to you or to themselves, or often both.

Improving Methadone Maintenance: Our methadone maintenance program, begun in 1968, is one of the oldest such units in the country. We quickly found that the inpatient induction method of Drs. Dole and Nyswander, in vogue at the time, was too costly and inefficient, and caused too many fights with the staff at the Connecticut Mental Health Center. The fights were over minor issues, such as bedtime for our addicts versus depressed patients, and major issues such as who stole the keys to the medication cabinet--it turned out to be an addicted nurse. The outpatient induction approach Bill Wieland was using in Philadelphia was inadequate clinically, since it did not appear to make a major dent in the lifestyle issues. This led us to pioneer a day induction technique (Kleber 1970), still in use in New Haven and elsewhere. Individuals judged to need such an intensive approach come in daily for four to six weeks when they start methadone. Issues dealt with are diverse: getting to the program on time, vocational readiness, use of leisure time, breaking the code of the street, and learning to deal with acting-out behavior that would get them quickly fired from jobs. Over the decades, the day technique made a very important contribution to the success of the methadone program, and could be usefully adopted elsewhere. The New Haven methadone program differed from many other such programs in the country in insisting on a high level of psycho-social rehabilitative efforts and involving patients with clinic governance. Because of the unique overall structure of the DDU, in which senior staff from methadone met on a regular basis with senior staff from Daytop, it was perhaps inevitable that some of the therapy approach of the therapeutic community would gel reflected in the methadone program and, conversely, our therapeutic community became one of the few in the country that would accept methadone patients and allow them lo remain on methadone for a number of months, while they were in the rehabilitation program. The loyalty displayed by the patients and staff paid off in the late 1960s during the Black Panther trial days in New Haven when some of that group approached and insisted that we either close the clinic or see it burn down, because it was "cooling out the ghetto" and keeping real social changes from happening. We resisted the demand, our patients stayed loyal to us, and we remained open throughout the worst of the times, although there were some scary days when dispensing had to take place at other sites.

In the early 1970s when most methadone programs believed that individuals could not be successfully detoxified from methadone maintenance, we began our detoxification program and with follow-up studies, demonstrated it was possible for many patients to do so and to remain abstinent (Riordan, *et. al.,* 1976). Since many patients remained on methadone, however, for long periods of lime, I was concerned about the long-term safety of methadone, and with NIDA funding, developed a series of studies in collaboration with leading faculty at Yale Medical School to look at the effect of methadone on various organ systems, including the eyes, heart, kidneys, liver, and lungs. We also looked at the prevalence of affective disorders, the first of many collaborations with Myrna Weissman. Fortunately, the organ studies showed no long-term deleterious effects of methadone for up to five years (Kleber, et. al., 1980), while the mood studies did show a relatively high percentage of affective disorders. During this period of time in the early 1970s, we also developed the Drug Dependence Institute, which, at its peak, was training over a thousand teachers, probation officers, and school social workers a year from around the United States. In addition, we carried out one of the major studies on drug education, showing that the techniques then in use had liltle effect in changing actual drug using behavior of adolescents (Berberian, *et. al.,* 1976). The combination of all these endeavors led to the unit in 1975 receiving the Gold Achievement Award of the American Psychiatric Association for its treatment, research, prevention, and community endeavors.

Narcotic Antagonists: Our use of narcotic antagonists was a natural outgrowth of our clinical situation. There was clearly a group of addicts who did not want methadone maintenance and were not willing to enter a long-term residential therapeutic community, yet they failed miserably in an outpatient drug-free approach. This led us to be involved with narcotic antagonists, one of the first programs in the country to do so. In 1969, we first tried using very large doses of the short-acting antagonist naloxone, which, at an oral dose of 1000 mg/day, would provide an 18 hour blockade, and combined this with a day program to cover the unblocked hours (Pierson, *et. al.,* 1974). The lack of a full 24 hour block and the difficulty in continuing to get such huge doses of oral naloxone led us to look elsewhere for better agents. Jerry Jaffe had already reported on the potential use of cyclazocine (Jaffe and Brill 1966), and in 1971, we began research with this. A few years later, we published a double-blind placebo-controlled study that concluded cyclazocine was better than naloxone because of its 24 hour duration of action, and certainly better than placebo, but was not well accepted by the patients because of

undesirable side effects (Kleber, *et. al.,* 1974). In 1972, we were able to get hold of the newest antagonist, naltrexone, and began research with it. Our work (Hurzeler, *et al.,* 1976), along with studies done by a number of other key investigators, many of whom are in the audience today, led ultimately to its approval in 1984 by the FDA as an adjunct to the treatment of narcotic addiction. My early experience with naltrexone introduced me to the problem of getting pharmaceutical companies interested in developing medications for substance abuse. Naltrexone was developed by Endo, which was then bought by DuPont. The managers at DuPont in 1973 felt that there was no profit potential in the drug and planned to discontinue it. By involving the New York Times and the Washington Post in a threatened press conference which would have labeled DuPont "unpatriotic" for withdrawing this medication at a time when it could potentially become valuable for returning veterans addicted to narcotics, we were able to change DuPont's mind. The final link in the naltrexone story came shortly before the FDA approval in 1984, when the company suddenly learned no one had ever studied whether patients got tolerant to its narcotic blocking effects. In three months we were able to mount and carry out a study which showed that tolerance did not develop to naltrexone's opioid blockading effect even after regular use for up to two years (Kleber, *et. al.,* 1985). In addition to the pharmacologic aspects, we constantly struggled with trying to develop new methods of clinical delivery that would make the-use of the antagonist more likely to be accepted by patients (Kosten and Kleber 1984). Family therapy, under Ray Anton, for example, was shown to double the retention rate over a six month period (Anton, *et. al.,* 1981). I should also point out in terms of my ability to foresee future developments, that I have been predicting since 1977 that naltrexone would be available in a depot form within a couple years. Now that LAAM, which Jerry Jaffe had been encouraging since the late 1960s, has finally been approved by the FDA and brought to market, one can only hope that depot naltrexone will shortly follow.

Opiate Detoxification: Clonidine: My third area of research focus in the 1970s was the issue of detoxification from opiates, a long standing concern stemming from my two years at Lexington when I ran the Detoxification Unit. In spite of clinical improvement while on methadone, numerous patients, even when seemingly rehabilitated, had difficulty successfully detoxifying from it. We tried a variety of approaches: specialized detoxification groups, open detox, blind detox, short-term and long-term, and found that while some of these approaches led to somewhat higher success rates, none was very successful in getting patients to zero and from relapsing during the difficult early drug-free months (Kleber 1977). Our first major breakthrough came with the development of clonidine, the alpha-adrenergic agonist, in 1978 (Gold, *et. al.,* 1978). Our research was the first to show that clonidine, then marketed as an anti-hypertensive, could successfully treat the majority of symptoms of opiate withdrawal, the first non mu-agonist to do so.

The clonidine story has been told a number of times, often erroneously. Rather than just a triumph of rational pharmacotherapy, where one proceeded from the animal to the human (the confirming animal studies were done after the first human papers were published), it was a triumph of a training system in which Yale residents could spend time both in clinical programs and in basic laboratory and animal research. Bright residents became the "culture carriers", bridging the knowledge gap that clinical faculty on the one hand and basic faculty on the other, may not have possessed. In this case, the culture carrier was Mark Gold, a third-year psychiatric resident, who was spending time with our methadone program, helping me with our detox projects, and at the same time, working with Gene Redmond, who, with Rhesus monkeys, was using clonidine to decrease the activity of the locus coereleous and shed light on the mechanism of anxiety symptoms, work based on the pioneering single-cell studies of the locus by George Aghajanian. Mark hypothesized that the symptoms of narcotic withdrawal resulted from over activation of the locus coereleous and that clonidine, by diminishing this activity, might prove to be effective in narcotic withdrawal. Bootlegging from our other projects, we had Izola Hogan work with Mark and myself to see whether, indeed, clonidine would suppress withdrawal symptoms. It worked, and the first presentation was in fact at CPDD. Our findings came too late to meet the deadline for submission, but when I called Lou Harris and told him of our study, he graciously agreed to have the paper presented at the 1978 meeting in Baltimore. Studies carricd out at Yale and elsewhere over the next seven years refined the method, showed it could be used for both heroin and methadone withdrawal, demonstrated its strengths and weaknesses, and established it as a widely-accepted alternative to the gradual reduction of methadone dose, the standard technique (Gold, *et. al.,* 1980; Charney, *et. al.,* 1981; Kleber, et. al, 1985; plus many others). It is now used in many countries, as well as in the United States, and enables one to markedly shorten the duration of

withdrawal from methadone maintetenance from mouths to a few weeks. A study by Don Jasinski at the ARC showed that clonidine was as effective as morphine in decreasing the physiologic signs of morphine withdrawal, but less successful in decreasing the psychological symptoms (Jasinski, *et. al.,* 1985).

As an aside, I should note that the company that makes clonidine was less than enthusiastic when I first informed them of our findings. In an attempt to get bridge funding while we waited for a NIDA grant, I called the company and asked for a small sum to carry out the research. The response of the corporate executive was, "you SOBs are going to ruin a $50 million anti-hypertensive market". He was conderned that the drug would get stigmatized as a treatment for addicts, that company representatives would be reluctant to carry it for fear of being mugged, hypertensive patients would not take it because of its association with addiction, etc. I cite this, which occurred in 1979-1980, as another example of what 15 years later, we are still eucountering in getting the pharmaceutical industry to be interested in developing medications for the treatment of addictions because of the stigma. The company later did a 180 degree reversal and provided funds for a multi-center study of clonidine for withdrawal. While clonidine has proved to be a useful agent clinically in withdrawal from opiates, and especially in serving as a bridge between methadone and naltrexone, its greatest importance ultimately may lie in the stimulation of research into the mechanisms underlying narcotic withdrawal that it produced.

For our work with clonidine, Aghajanian, Gold, Redmond, and I received in 1981 the American Psychiatric Association Foundation's Fund Prize for psychiatric research, the highest award the APA gives, and, until this Eddy Award, the one of which I was most proud.

Opiate Detoxification: Ultra-Rapid Detoxification: While the clonidine technique shortened the time for methadone withdrawal, it did not do so for heroin withdrawal. There seemed to be no long-tenn benefit in terms of a higher percentage of patients able to remain drug-free, even though it did eliminate the rebound that usually follows methadone detoxification. In 1980, a patient came to me from our methadone program. He had received an excellent job offer but in an area where methadone maintenance was not available. In order to get the job, he would have to start in a week. How was one going to get him off his dose of methadone in one week? Charlie Riordan and I put our heads together, reviewed the literature, saw that Richard Resnick had tried precipitated withdrawal in the 1970s but it was not well accepted by the patients because the agents to block the withdrawal were not adequate (Resnick, *et. al.,* 1977). Now, however, we had clonidine, and so began the ultra-rapid withdrawal method using a narcotic antagonist, naltrexone, and blocking the precipitated withdrawal with clonidine (Riordan aud Kleber 1980). We got our patient down to 50 mg of methadone in a few days and then did the rapid detoxification. A week later, he was able to start his new job and was on naltrexone for the first few weeks to see him through any craving that might occur. Unfortunately, I do not know the long-term outcome of that story, whether he was able to stay off opiates and maintain the job. Working out the details of the method took a number of years to ensure that the procedure was safe and well-tolerated, work done with Dennis Charncy, Tom Kosten, and Eugenia Vining (Charncy, *et. al.,* 1982; Charney, *et. al.,* 1986; Kleber, *et. al.,* 1987; Vining, *et. al.,* 1988). The procedure now takes only 48 hours from the first naltrexone dose of 12.5 mg until the maintenance dose of 50 mg is given.

The technique is a simple one. On day one, the individual is pre-treated with clonidine aud then an hour later, is given 12.5 mg of naltrexone; for the rest of the day he is given prn clonidine, and a benzodiazepine to treat unrelieved symptoms, such as tnuscle cramping of anxiety. We do this the first day as a day procedure, keeping the patient around from about nine to five. Twenty-four hours after the first dose, the patient is again pre-treated with clonidine and then given 25 mg of naltrexone and is able to leave a few hours later, with pm clonidine. Interestingly, the amount of clonidine necessary on the second day is substantially lower than the first day. It appears that once you have taken the exogenous opiate off the receptor, if you keep it off, giving more naltrexone does not precipitate more withdrawal symptoms. Forty-eight hours after the first dose, the individual is again pre-treated with clonidine, given 50 mg of naltrexone an hour later, and can leave shortly thereafter, basically withdrawn and maintained on naltrexone. Some patients may need low doses of clonidine for the next couple of days. The technique is of theoretical interest in that it equalizes the duration of withdrawal of long-acting and short-acting opiates. I have used it in people maintained on up to 50 mg a day of methadone, and essentially any dose of heroin or prescription opiates. Brewer, in England, has shortened the procedure to 18

hours by giving larger doses of naltrexone (Brewer 1988), and Loimer, in Austria, and others have shortened it to six hours by keeping the person under general anesthesia and giving higher initial doses of naltrexone (Loimer 1991). I do not like this latter procedure because I believe that, since opiate withdrawal is essentially a painful but not life-threatening event, one should not use techniques involving general anesthesia which has the potential to be life-threatening. It also would be incumbent upon researchers carrying out those procedures to look at the risk/benefit ratio. The recent study done at Yale 'by O'Connor showed a 90% success rate for clonidine/naltrexone, as far as completing detoxification, compared to only about 40% with the traditional clonidine method (O'Conner, *et. al.,* 1992). However, at the end of 30 days, the two groups were about equal as far as the percentage of patients still in treatment, which has to be the ultimate benefit. In these days of short stays and managed care, the ultra-rapid detoxification method appears to have increasing advantages, and I have received more calls about it in the past six months than I did in the last five years.

Psychopathology and Addiction: Our long-term study of methadone safety also showed the high prevalence of affective disorders in these methadone-maintained patients, leading to our interest in pursuing the whole issue of psychopathology and addiction, often in collaboration with Myrna Weissman. In the late 1970s, we were awarded a major grant from NIDA to look at psychiatric diagnosis, symptoms, neuro-psychological impairment, and ego functioning in over 700 opiate addicts. This study, the largest and most definitive done up to that time, was, for many years, the benchmark for such findings (Rounsaville, *et. al.,* 1982-a; Rounsaville, *et. al.,* 1982-b, plus many others). One particular finding that interested me was the study of 100 opiate addicts who had never sought treatment: to try and understand the similarities and differences between them and treatment seekers. The principal finding of the study was that the untreated sample had much less in the way of psychopathology than those who were seeking treatment (Rounsaville and Kleber 1985). These major epidemiologic studies were carried out under the direction of Bruce Rounsaville, who had just joined us after his psychiatric training at Yale, and is now one of the leaders in substance abuse research in the United States and Director of the NIDA-Yale Center on Psychosocial Research.

In the early 1980s, Tom Kosten, who had completed his psychiatric residency at Yale, joined SATU and has gone on to become one of the leading researchers in psychopharmacologic aspects of substance abuse and director at Yale of the NIDA Center for Medication Development. He and Bruce are perfect compliments to each other, Bruce being the leading authority on epidemiologic, diagnostic, and pscyhotherapeutic trials, and Tom, the consummate expert on psychopharmacologic approaches. Tom played a major role in the 1980s in our studies with buprenorphine as a potentiaI alternative to methadone and the medication trials for cocaine treatment, as well as the critical intermediary between our unit and the biologic studies units at CMAC Yale and the VA; being the main culture carrier to scientists such as Eric Nestler, George Aghajanian, Dennis Charney, and others in that excellent group. During this decade when various proponents were arguing for their approach to understanding and treating addiction, the emphasis in my talks and writings was that agents such as naltrexone and methadone were medications, not treatments, and needed to be combined with psychosocial supports. At the same time, I argued that psychology alone was inadequate to explain drug abuse and needed to be combined with a greater understanding of neuro-pharmacologic and other biologic and genetic factors. This emphasis on both areas was mirrored in the multi-dimensional approaches being developed in my treatment and research units.

Cocaine: By 1982, cocaine abuse was becoming a major public health problem in New Haven as well as the rest of the county, and it was quickly apparent that there was no adequate treatment for it. Our Yale group became the leader in systematic pharmacologic methods that might increase the success of such treatment. The first seven years of this took place under the inspiration of Frank Gawin, who had also completed his psychiatric residency at Yale, and then, when he left for UCLA, by Tom Kosten. Our early attempts at treating cocaine were based on our models of treating heroin addiction. Instead of methadone, we tried methylphenidate, which bore a similar relation to cocaine as methadone did to heroin: it was orally effective, longer acting and produced less euphoria. Unfortunately, it was not methadone--and though it proved to be effective in treating cocaine abusers who had Attention Deficit Disorder (Khantzian, *et. al.,* 1984), in individuals without such a diagnosis, it appeared to serve primarily as a cue to more cocaine use (Gawin, *et. al.,* 1985). We tried lithium as a naltrexone model, since there was animal literature showing that it could block the effects of amphetamines. Unfortunately, it, too, did not pan out, although it was of use in treating bi-polar cocaine abusers (Kleber and

Gawin 1986). Desipramine, our third drug, seemed to be useful for cocaine addicts, even those without an affective disorder. The trial was initiated because of our theory about the effects of chronic cocaine on regulation of the dopamine receptor and the similarity of the effects produced to that of the chronic depressive state (Gawin and Kleber 1988). The open clinical trial was followed by a successful double-blind placebo-controlled trial, with desipramine reducing both craving and use (Gawin, *et. al.,* 1989). It remains the best-studied drug for the treatment of cocaine addiction, but, unfortunately, there arc both positive and negative studies. In retrospect, it appears that desipmmine may indeed be useful for the group of cocaine addicts we studied in the mid-1980s, namely the middle- and working-class individuals taking cocaine by the intranasal route, but its effectiveness may be overwhelmed, both by the social pathology of crack addicts as well as by the smoked and injected routes of administration. Marian Fischman has shown in the human laboratory that desipramine decreases the positive subjective effects of cocaine and cocaine craving without, however, decreasing the frequency of use (Fischman, *et. al.,* 1990). If one has an individual with other social supports--a job, a family, etc.--the decreased hedonic value of the cocaine may he sufficient to help him give up the habit. With the faster routes of administration and the presence of less social support, this desipramine effect may not be adequate. Frank's clinical experiences with cocaine addicts led to a theory of a cocaine withdrawal syndrome (Gawin and Kleber 1986) which has support from clinicians treating outpatient cocaine addicts, but has not been continued in inpatient settings--the difference perhaps relating to the availability of cocaine and cocaine-related cues in the outpatient world. Our work with cocaine was aided throughout by the research skills and knowledge of stimulants of Bob Byck, who had been studying cocaine long before I ever encountered the drug.

The failure of medication to adequately treat cocaine intensified our search for non-pharmacologic approaches. Advances included the work of Bruce Rounsaville with Myrna Weissman in developing interpersonal therapy for cocaine abusers, and the work of Kathleen Carroll on relapse prevention for stimulant and alcohol abusers. Kathy has now become one of the leaders in relapse prevention, writing the manual on this for Project Match. At the same time, Stephanie O'Malley was running our alcohol program and beginning her pioneering work with naltrexone in alcoholism, which, along with the work at Pennsylvania which had precedence, were the two key studies on which the FDS based its approval of naltrexone for the treatment of alcoholism in December, 1994. Although the Pennsylvania group under Volpicelli had originated the naltrexone project, Stephanie's work added an important dimension by showing the differential outcome effect of using a coping skills strategy in comparison to the supportive approach.

Researchers: This superb group of clinical researchers at Yale--Carroll, Gawin, Kosten, O'Malley, Schottenfeld, Riordan, and Rounsaville--are better at originating new ideas, writing the grants to get the support, carrying out the studies, and writing up the papers than any group I have encountered. Their skills and personalities complimented each other and made our Yale group during the decade of the 1980s and well into the '90s, the most productive in the country.

1980s and ONDCP: The decade of the 1980s was an extraordinarily productive one, not just for SATU clinically and in research, but also for me personally: serving on numerous editorial boards; winning a number of awards; serving on the FDA Drug Abuse Advisory Committee, which was easy since during my whole three years on it, it never met; being a member of the Executive Committee of CPDD, which was not easy because each meeting seemed to last for three years; serving on the IOM committee that evaluated treatment; giving hundreds of lectures at medical schools, psychiatric societies, and in foreign countries; serving on the Board of Scientific Counselors at the ARC; heading the mayor's task force on drugs; beginning in 1986, the NIDA-funded clinical research center for opioid and cocaine abuse; and developing in 1988 the first NIDA-funded center to train psychiatrists for research carreers in substance abuse. By 1989, SATU was treating over a thousand patients a week for various substance abuse problems and carrying out over 20 research studies. I thought that the rest of my career was going to be happily spent at Yale working with the superb staff we had assembled and carrying out important research and treatment.

That all changed in February, 1989, when I was called by the Office of National Drug Control Policy, a new oftice just set up in the White House, and was asked to interview for the position of Deputy Director for Demand Reduction. Since I couldn't make it to Washington that week, we agreed to meet in New York, where

the Director, 'Drug Czar' Bill Bennett, was giving a talk. We spent two hours at a hotel bar talking and at the end of that time, Bill offered me the position. Given how well things were going at Yale, I was extraordinarily ambivalent about leaving and asked for a week to think it over. One of my first calls was to Danny Freedman, explaining that now was not a good time to leave. Danny gave me his usual succinct advice, "Herb, when it is a good time for you, they either won't offer you the job or you won't want to do it." Sage advice; I accepted it, and then experienced during the next few months one of the more interesting periods in my life while waiting for the final nomination for the position by President Bush, which occurred in June. During these months there was an FBI background check involving interviews with over 70 individuals, as the position carried a 'top secret' security clearance; support from numerous medical, scientific, prevention and educational groups and individuals; fierce opposition from a few groups who claimed I was "soft on drugs"; interviews with White House staff, who wanted to know why I should get such a position since I hadn't campaigned for the President or donated money; and a potential Washington Post leak. What overcame all those obstacles, the full discussion of which would be an article itself, was the persistence of Bill Bennett. Bill was dedicated to getting the job done, felt that I could be of help to him in this, and worked had to make sure that my nomination became a reality. From March to June, I commuted between New Haven and Washington, trying to help in the setting up of the office while still carrying out my Yale duties, and finally, in July, moved to Washington full time.

I was confirmed by the Senate, August 1, 1989. Near the end of my confirmation hearing, before the Senate Committee on Labor and Human Resources headed by Senator Kennedy, I was asked how I managed to remain optimistic after 20 years in the field. I replied that what inspired me was a quote from the Talmud, *"The day is short; The task is difficult; It is not possible to complete it, But we are forbidden not to try."* That ended the hearing on a very upbeat note. My Yale staff wanted to frame the quote as a present, but, unfortunately, Roz Liss went back to the Talmud and found I had misquoted it; I had left out the third line, *"The workers are lazy."* I, of course, had no intention of quoting that line at the hearing. As a result, the quote that hangs on the wall of my office now, as well as all during my ONDCP days, is my version with the caption underneath, 'The Talmud--as misquoted by Herb Kleber".

I could give a lecture at least as long as the one today on what happened during the next two and a half years in the White House. They were wonderfully exciting and heady years, and difficult ones as well. We accomplished a lot and had many frustrations. My favorite saying became one that I heard early on, "Welcome to Washington, where the motto is: we'll double cross that bridge when we come to it". I learned how government could operate when it is at its finest, and how often it doesn't achieve that. Again I had the good fortune to find talented colleagues to help in carrying out our important mission--individuals such as Phil Diaz, Linda Lewis, Arthur Houghton, Rich Harwood, Scott Hamilton, Dan Schechter, Ingrid Kolb, Donna Rigby, and Misty Church. Space is too short to go into details, so I will simply mention some of the accomplishments I assisted in during those two and a half years of which I am most proud: funding for treatment and prevention of drug abuse from the Federal government doubled; the community partnership program at OSAP, which now funds over 200 such programs across the United States, was begun; the treatment campus projects; the Job Corps Drug Treatment Program that I pushed at the urging of Jerry Jaffe; the opening up of OTI, not CSAT, and its launching by the eloquent Beny Primm; the Target Cities program; the defense of methadone maintenance as an important treatment modality, when the White House Conference on Drug Abuse in 1988 had sharply criticized it; the championing of the role of NIDA and its research mission when it came under frequent attack; the strengthening of the NIDA Medication Development Division, with the special help of Senators Biden, Hatch, and Moynihan.

Major disappointments included the inability to get funded a national volunteer program, which would have put individuals into communities throughout the United States to assist with prevention programs and treatment, the inability to expand treatment adequately to meet the needs, and to equalize the percentage of the budget going to demand and supply reduction. One of my final acts was to develop a program, a $1 billion initiative for expanding treatment and prevention, which I had hoped President Bush would release and which I believe he favored, but OMB blocked. The office had, in one sense, enormous power, but also limitations getting the VA to adequately focus on treatment of drug abuse being one of them. Another final act was to work with Bill Roper at CDC to get them to initiate the study on needle exchange, which was carried out at the University of

California, although I personally have major doubts and concerns about needle exchange, both in theory and effectiveness. My belief at ONDCP, as well as now, is that important government policy should be driven by science, and that if the government is to make hard decisions in this area, it should be informed by the best research possible. I oflen had difficulty getting this view accepted (Kleber 1992, Kleber 1993). I constantly demonstrated with the Department of Education that they were not adequately evaluating the $500 million a year that was going into the drug-free schools program, and warned them that, sooner or later, Congress would cut the funds because they could not show the money was well spent. Sure enough, the current Congress has called for total elimination of the program. After Bill Bennett left ONDCP in November, 1990, much of the fun and the ability to get things done left with him, and in the fall of 1991, I decided to return to academia.

Columbia and CASA: When I left ONDCP in November, 1991, I came to New York to begin two new careers. First, as Professor of Psychiatry at Columbia and the New York State Psychiatric Institute, where, working with Marian Fischman, we have created a new Division on Substance Abuse. The division has already begun a clinical research training fellowship, a medication development center to develop new agents to treat cocaine and heroin addiction, and many individual grants. We have begun to train some promising young faculty and look forward to helping to train the new leaders in the field. Second, my other career is as Executive Vice President and Medical Director of the Center on Addiction and Substance Abuse (CASA) at Columbia, a policy center that Joe Califano, Jr., the former secretary of HEW under President Carter, and I founded in October, 1992. CASA is a policy research center, dedicated to advancing awareness of the tremendous cost that American society pays for the problem of substance abuse (including alcohol and tobacco as well as the illicit drugs), and increasing knowledge of the most effective approaches to prevention and treatment so as to make these endeavors more acceptable and saleable to the public and policy makers. My most recent project at CASA, with the collaboration of Tom McLellan, is a comprehensive evaluation of the national treatment system, inlcuding evaluating 300 programs and 3,000 patients for a year.

Concluding Remarks: A recent paper by Dr. David Nathan, the Chair of the NIH Director's Panel on Clinical Research, commented on the passing of the "triple threat" physician: the teacher, clinician, investigator. He attributed the change to the increased complexity of both clinical work and research, making it difficult for individuals to be skilled in both. I consider myself fortunate lo have lived through the simpler times of the last three decades when it was indeed possible to carry out all three activities, and to have been blessed with young colleagues who could keep me at the cutting edge of knowledge and techniques. In my new incarnation al Columbia and CASA, I hope lo continue being a triple threat. In that sense, I see the Eddy Award not as the culmination of my career, as some of my very distinguished predecessors have noted, but more the highlight of my career to date--a career which I hope will have many more fun and productive years. If one takes one's patients and one's science seriously, but not oneself, the process of research can be an extraordinarily rewarding one.

I believe that although these next few years will be difficult national ones with diminished funding for research and treatment, good science and good treatment will survive, and the setback in funding will be a temporary one. Thank you, again, for the honor you have done me. I am reminded of the words of John Stuart Mill: *"Those only are happy who have their minds fixed on some object other than their own happiness; on the happiness of others, on the improvement of mankind, even on some art or pursuit, followed not as a means, but us itself an ideal end. Aiming thus at something else, they find happiness by the way."*

MOLECULAR MECHANISMS OF THE BRAIN REWARD SYSTEM

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The focus of the symposium entitled "Molecular Mechanisms of the Brain Reward System" was on the functional mechanisms of the brain reward system in relation to drugs of abuse, describing their neuroanatomical loci and their underlying neurophysiological, neurochemical, and neuropharmacological mechanisms. The main emphasis was on the role of dopamine in brain reward mechanisms, dealing with such topics as the neuroanatomical-neurophysiological mapping of the brain reward system, the molecular biology of the dopamine reuptake system, the nature of the dopaminergic receptor subtypes involved in reward, behavioral studies with dopamine receptor knockout mice, and a discussion of alternate mechanisms involving ion channels.

Donald J. Woodward - Brain Mapping of the Brain Reward System. One objective of brain mapping of the reward system is to define the organization and functional role of all the biological structures involved in behaviors leading to drug self-stimulation. The brain reward system consists of an extensive set of interconnections between cortex, dorsal and ventral striatum, palladium, ventral tegmental area, amygdala, and other areas. A prevailing hypothesis is that behaviors leading to drug self-administration involve a sequential activation of signals which may originate in frontal cerebral cortex, and propagate through a system of nested cortico loops. These drive the task segments of the drug seeking behavior. The goal of ensemble neurons recording electrophysiology is to map the sequential signals in these loops that translate "incentives" and "craving" motivational activity into drug seeking behavior, and to understand the basis for neurochemical compartmentation.

Three-dimensional computer visualization, new database techniques for documents, graphical data and other information, and modern use of Ethernet to facilitate communication is likely to provide indispensible intellectual tools to allow synthesis of information. The overlapping distribution of distinct neurophysiologica! neuron ensemble activity patterns suggests a complex mode of connectional organization related to the high diversity of neuronal behavioral correlates found between neighboring neurons in a narrow region. Individual dendritic fields of adjacent neurons achieve high specificity by selecting arbitrary sets of connections from the diverse afferents that project to and overlap within compartments in the rat nucleus accumbens. Future mapping studies will need to determine the molecular mechanism operating to specify which differentiation may reflect a set of high specific pharmacological sensitivities of individual task components of both routine behavior and of drug self-administration. This information will be needed to interpret altered behavior after studies of gene and drug action on identified neuroanatomical receptor distributions.

Susan G. Amara - Molecular Biology of the Dopamine Transporter. At the plasma membrane of both neurons and glial cells, specialized sodium-dependent carrier proteins mediate the removal of neurotransmitter from the extracellular space. Drugs that block neurotransmitter re-uptake potentiate neurotransmission, often with dramatic physiological and behavioral consequences. Thus, the transporters for the mono-amines--dopamine, norepinephrine and serotonin-- are the primary targets for psychomotor stimulants including cocaine and amphetamines, as well as for a variety of therapeutic antidepressants. Several years ago our laboratory used an expression cloning strategy to identify the first cDNA encoding a cocaine-sensitive mono-amine transporter, the human norepinephrine transporter (NET). The sequence of this cDNA has served as the basis for identifying several other members of the same gene family, including the dopamine transporter which has been proposed to be the most significant site of action for the euphoric and addictive effects of cocaine.

Using the two cloned catecholamine transporters we have actively explored the hypothesis that the interaction of cocaine with DAT has unique properties which distinguish it from NET, and are fundamental to the

addictive potential of cocaine. In these studies we have demonstrated that there are differences in the regional distribution, kinetics, and mechanistic properties between the two transporters. Using an approach that has allowed us to generate a random series of DAT/NET and NET/DAT chimeras, we have examined domains in DAT that contribute to its kinetic and pharmacological properties. We have also begun to use electrophysiological techniques to measure currents generated by the movement of substrates and co-transported ions and to determine how various drugs influence these currents. Establishing the structural and functional relationships between the sites where substrates, ions, and drugs interact with the transporter is likely to be important in understanding the unique impact of cocaine on the dopamine transporter and may provide a basis for the design of drugs which block the binding of cocaine, but do not interfere with the transport of dopamine.

Lisa H. Gold - Molecular Mechanisms of Drug Reward. Technological advances have resulted in the development of gene targeting technique by which specified changes are introduced into the nucleotide sequence of a chosen gene. In particular, knockout mutants that possess an inactivation of genes thought to mediate biological and/or pathobiological processes are becoming valuable tools to examine the functions of a variety of gene products. Recently, mice deficient in various neurotransmitter receptor subtypes and second messenger molecules have begun to be used to investigate the molecular basis for the behavioral actions of drugs of abuse. The brain dopaminergic system is a critical modulator of basal ganglia function and plasticity and has been associated with the behavioral actions of various psychoactive drugs. To investigate the contribution of the dopamine-1 (D1) receptor to this modulation, gene targeting technology was used to generate D1 receptor deficient mutant mice (Xu, *et. al.,* 1994). The most prominent neuroanatomica1 phenotype of the D1 receptor mutant mice is an undetectable dynorphin striosmal system in the caudoputamen. In contrast, Nissl staining, immunostaining, and ligand binding indicate that tyrosine hydroxylase, DARP-32, calbindin, D2 receptors and dopamine transporter distribution are qualitatively normal, while some disturbances in substance P and enkephalin systems are evident. Functional consequences of D1 receptor inactivation in mutant mice were assessed in behavioral studies conducted under basal conditions and following pharmacologic challenge with various dopaminergic agents. When tested during the dark portion of the light/dark cycle, mutant mice were hyperactive compared to wild-type mice. D1 receptor mutant mice were non-responsive to the motor stimulant effects of the D1 agonist, SKF 81297, and the motor suppressive and cataleptic effects of a D1 antagonist, Sch 23390. These results provide a functional confirmation of the absence of D1 receptors in the mutants and suggest selectivity of these ligands for the D1 receptor in the dose ranges studied. Although D1 receptor mice were less sensitive to the motor stimulant effects of amphetamine, they exhibited stereotyped motor activity and sensitization following repeated amphetamine treatments. However. amphetamine-incducced increases in rearing were completely abolished in the mutant mice. Thus, an indirect D1 receptor agonist was able to stimulate locomotion in D1 receptor mutant mice and the development of sensitization to locomotor stimulation does not seem to require the presence of the D1 receptor.

In addition to unconditioned behaviors, mice can also be tested in procedures traditionally used to examine conditioned behaviors. Intravenous drug self-administration is an animal model for the reinforcing effects of drugs. Operant responding for food can be used to examine the selectivity of behavioral responses for drugs versus non-drug reinforcers. Mice trained to perform a nosepoke operant for either food or drug reinforcement respond in systematic ways to manipulations of experimental contingencies. Studies examining the behavior of D1 receptor mutant mice in cocaine self-administration and operant responding for food procedures are ongoing.

In sum, D1 receptor mutant mice are valuable for exploring dopaminergic functions related not only to motor behavior, but also to those behaviors associated with natural reward, reinforcing properties of drugs, and learning processes. (Xu, M.; Moratalla, R.; Gold, L. M.; Hiroi, N.; Koob, G. F.; Graybiel, A. M.; and Tonegawa, S.) Loss of dynorphin-immunostaining in the striatum and locomotor hyperactivity in dopamine one receptor deficient mice. (Cell, 79:729-742, 1994)

Leo G. Abood - Overview and New perspectives. After a brief review of the pharmacology of cocaine, cocaine antagonists, and the mechanisms involving dopamine as well as other neurotransmitter systems, Abood described other mechanisms implicated in the action of cocaine and nicotine. The alternative mechanisms involved the direct action of cocaine and nicotine on ion channels, specifically Na and Ca. A series of synthetic cocaine analogs were compared for their effectiveness in antagonizing the behavioral effects of nicotine in mice with their ability to compete for ([^{3}H]mecamylamine (an ion channel probe for nicotine receptors), [^{3}H]nicotine, and [^{3}H]-3-quinuclidinylbenzilate) binding to calf brain membranes. Within a series of phenyltropane carboxylic acid methyl esters, the most potent antagonists were the 4-I and 4-F-phenyl analogs, while replacement of F by Cl or alkyl groups diminished potency. The isopropyl and phenylcarboxylic acid esters were comparable in potency to the methyl esters. There appeared to be a relationship between the potency of the analogs in inhibiting me dopamine transporter and nicotine antagonism. A good correlation was observed between pharmacologic potency and [^{3}H]mecamylmine binding to brain membranes. It was concluded that the antagonistic action of the cocaine analogs involved an ion channel site on the neuronal nicotinic cholinergic receptors (nAchRs). An irreversible allosteric inhibitor of brain nicotinic cholinergic receptors, 1,2,2,6,6-pentamethyl-4-isothiocyanopiperidine, irreversibly inhibited [^{3}H]mecamylamine binding to brain membranes in the mM range without affecting the binding of [^{3}H]methylcarbamylcl~oline, a prototypic ligand for nAChRs. It antagonized nicotine-induced seizures in mice; and a single dose blocked nicotine's pharmacological effects and inhibited whole brain [3H]mecamykamine binding for over 18 hours. The ligand also blocked the pharmacological effects of cocaine in mice, presumably by blocking cocaine's action on ion channels.

In an effort to investigate the hypothesis that nicotine may be acting at ion channels, studies were undertaken on cultured rat ventricular myocytes which are devoid of parasympathetic or sympathetic innervations as well as nAChRs ([^{3}H]nicotine binding studies on rat ventricular membranes). With the use of the fluorescent Ca2+ indicator fura 2, 50 μM nicotine was shown to decrease the rate of spontaneous Ca2+ transients (a measure of heart rate). Exposure of the isolated rat myocytes to 10 μM of either 4-pempidineisothiocyanate or 5-isothiocyanonicotine irreversibly blocked the nicotine-induced inhibitory action on contraction and Ca2+ transients. Preliminary studies using patch clamping techniques indicate that 10-100 μM nicotine inhibits Na currents (Ina) of myocytes. Laser flash photoylsis studies on cell lines transfected with nAChRs revealed the presence of a cocaine inhibitory site on me nAChR ion channel. The findings indicate that nicotine acts on ion channels independently of its action at nAChR.

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MOLECULAR AND BIOCHEMICAL EVIDENCE FOR RECEPTORS FOR DRUGS OF ABUSE ON IMMUNE CELLS

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Drugs of abuse including opiates and cannabinoids have been found to affect functions of the immune system. For example, morphine given *in vivo* suppresses many immune functions *in vitro,* including antibody formation by spleen cells, splenic mitogen responses and NK cell activities. In addition, cannabinoids have been shown to modulate (suppress in most cases) immune responses *in vitro.* In this symposium, evidence was presented for the presence of receptors for opioids and cannabinoids on cells of the immune system.

J. M. Bidlack: RECEPTOR BINDING STUDIES TO CHARACTERIZE OPIOID RECEPTORS ON IMMUNE CELLS

Opioid receptors have been difficult to detect on mixed lymphocyte populations by the use of receptor binding assays. Possible reasons include: 1) Opioid receptors are expressed on only a small subpopulation of lymphocytes; 2) The expression of opioid receptors on lymphocytes may change during lymphocyte maturation; and 3) Receptor binding methodology is not sufficiently sensitive to detect receptors present at a low density. Because of these problems, we screened lymphoma cell lines, a homogenous population of cells, for opioid receptors. The mouse thymoma cell line R1.1 and derivative cell lines express a κ opioid receptor that is negatively coupled to adenylyl cyclase through a pertussis toxin-sensitive G protein (Bidlack *et al.,* 1992; Lawrence and Bidlack, 1993; Lawrence *et al.,* 1995a). This lymphoma κ receptor is identical to the brain κ_1 opioid receptor in binding and G protein coupling characteristics. These studies demonstrate that a cell from the immune system can express a brain-type opioid receptor.

In order to detect opioid receptors on mixed lymphocyte populations, an indirect immunolluorescent method that is more sensitive than radioreceptor binding assays was developed (Lawrence *et al.,* 1995b). A fluorescein-conjugated κ opioid with a structure similar to U50,488 was synthesized. To amplify the signal, a biotin-conjugated anti-fluorescein antibody was added, followed by extravidin-conjugated phycoerythrin. The extravidin bound to the biotin and phycoerythrin is a fluorophore that has a fluorescent intensity at least 20-fold greater than fluorescein. Using this method, the thymoma cell lines and mouse C57B1/6By thymocytes have been labeled. This labeling was blocked by the inclusion of excess nor-binaltorphimine, indicating specific labeling of the κ opioid receptor. (Supported by USPHS grants DA04355 and DA07232 from the National Institute on Drug Abuse)

L.-Y. Liu-Chen and T. J. Rogers: EXPRESSION OF κ OPIOID RECEPTOR mRNA ON IMMUNE CELLS

R1.1 cells exhibit a $CD4^-$, $CD8^-$, $CD3^{Low}$ and $CD25^{Low}$ cell surface phenotype. Thus, R1.1 cells represent thymocytes in one of the early stages of differentiation. Poly (A^+) RNA was extracted from R1.1 cells. Reverse transcription-polymerase chain reaction (RT-PCR) was performed with four pairs of primers derived from the sequence of the cloned mouse κ opioid receptor (Yasuda *et al.,* 1993). These primers amplified the following fragments: 111-706, 645-1042, 774-1376 and 111-1376, respectively. PCR products were subjected to agarose gel electrophoresis and Southern blot analysis. Positive bands were cloned into the pGEMT vector and nucleotide sequences determined. Two cDNA sequences of the κ receptor have been identified. One is identical to the previously cloned κ receptor, whereas the other has a 30-bp insertion at 15 bp upstream from the initiation codon. This 30-bp sequence is present in the genomic sequence. Since this insertion is in the 5'-untranslated region and it does not contain any initiation codon, the amino acid sequence of the receptor is unchanged. Whether this 30-bp fragment plays any role in the level of expression of the

receptor remains to be determined (Supported by USPHS grants DA 04745 and DA06650 from the National Institute on Drug Abuse)

T. W. Klein: MOLECULAR APPROACHES TO IDENTIFYING CANNABINOID RECEPTORS ON IMMUNE CELLS

Evidence suggests the existence of a cannabinoid neurotransmitter system containing endogenous cannabinoids such as anandamide and at least three cannabinoid receptor subtypes termed CB1, CB1A. and CB2. These subtypes are found in both neural and immune tissues; however, the precise distribution pattern and function is not understood. We show, using RT-PCR and competitive binding assays, that CB1 mRNA and cannabinoid-specific binding sites are found in varying amounts in mouse leukocyte subsets with B cells > T cells > macrophages. Furthermore, stimulation of lymphocyte and macrophage cultures with mitogens increases the levels of mRNA and binding sites, suggesting CB1 receptor expression increases with immune cell activation. Finally, using a polyclonal antibody to a CB receptor peptide, we show by Western blotting three immunoreactive bands which are increased by mitogen activation These results suggest CB1 receptor expression may be linked to the level of immune cell activation and therefore may be both necessary for immune cell regulation and available for cannabinoid-induced immunomodulation. (Supported by USPHS grants DA03646 and DA07245 from the National Institute on Drug Abuse)

J. J. Madden: THE EXPRESSION OF MORPHINE-BINDING SITES ON HUMAN T LYMPHOCYTES

We have used two assays - the repair of UV damage to DNA and the enumeration of active sheep erythrocyte (E) rosettes - to define a role for a morphine receptor on the human T lymphocyte. Based on both *in vitro* and *in vivo* morphine exposure, the receptor mat elicits these responses has the following characteristics: high affinity (K_d - 1 nM); stereospecificity; naloxone reversibility; and a presence on a significant proportion of the peripheral T cells (>70%). None of the known morphine binding sites exhibits all of the properties defined by these assays. The cloned μ receptor is either totally absent from these cells or found only in an exceedingly small percentage of the cells (<1%). RT-PCR (35 cycles) failed to demonstrate the presence of the μ receptor mRNA by either ethidium bromide or radioactive labeling - methods that would have found 1 in 10^6 or 1 in 10^8 mRNA molecules in the total RNA pool, respectively. The morphine binding site found on activated T cells is not stereospecitic, and for that and other reasons is eliminated from contention as the binding sites responsible for the DNA repair and E rosetting data. The mu_3 morphine binding site lacks stereospecificity as well as avidity for morphine. These results suggest that yet another morphine binding site exists on human peripheral T lymphocytes and is responsible for at least several biological activities of morphine on these cells. This binding site may be part of the new family of immune opiate receptors. (Supported in part by USPHS grant DA05002 from the National Institute on Drug Abuse)

B. M. Sharp: OPIOID MODULATION OF IMMUNE FUNCTION: EVIDENCE FOR EFFECTS ON cAMP PRODUCTION, CELL PROLIFERATION AND NOVEL RECEPTORS

We have recently reported that several delta opiate receptor (DOR) agonists inhibited anti-CD_3-driven proliferation and IL-2 production by highly purified murine $CD4^+$ and $CD8^+$ T-cells (Shahabi and Sharp, 1995). These effects required pre-treatment with DOR agonists and were inhibited by naltrindole. Thus, quiescent splenic T-cells appear to express delta-like opiate receptors that modulate the T-cell activation program when initiated through the T-cell receptor. To further explore these findings, we have studied the expression of mRNA encoding neuronal DOR (n-DOR). RT-PCR analyses, Southern blotting and sequencing of a 355 nucleotide PCR product demonstrated the presence of low levels of n-DOR mRNA in unstimulated lymphocytes. Ethidium bromide detected n-DOR from unfractionated lymph node cells, whereas Southem blotting was required to detect n-DOR mRNA in purified splenic and lymph node-derived T-cells. N-DOR was also detected in the thymus. Activation of cells with anti-CD3 and IL-2 failed to significantly affect levels of n-DOR mRNA. Thus, low levels of n-DOR and mRNA are expressed by normal quiescent T-cells obtained from various lymphoid organs. Levels are relatively higher in total lymph node than spleen. The role of n-DOR mRNA in the expression of DOR-like receptors and in functional responses to DOR agonists by normal T-cells remains to be clarified.

The effects of ß-endorphin and SNC80 on cAMP production by T-cell enriched murine splenocytes were also studied. Splenocytes were depleted of B-cells and loaded with [^{3}H]adenine. Thereafter, cells were pre-incubated with opiates and then stimulated with forskolin for 15 min. ß-Endorphin enhanced forskolin-stimulated cAMP production in a dose-dependent manner (140-160% of control at 10^{-7} M). This was blocked by naltrindole and the more hydrophilic analog, glycine-naltrindole. Similarly, SNC80 enhanced forskolin-stimulated cAMP production and this was also blocked by naltrindole. Increasing pre-treatment intervals were associated with reduced efficacy of either ß-endorphin or SNC80. Thus ß-endorphin or SNC80 activated DOR-like receptors on B-cell depleted splenocytes, resulting in enhanced forskolin-stimulated cAMP production. The mechanism(s) whereby DOR-like receptors on mononuclear cells amplify cAMP production and the effects of this on cell proliferation and cytokine production are currently under investigation. (Supported by USPHS grant DA04196 from the National Institute on Drug Abuse)

C. J. Evans: ANALYSIS OF OPIOID RECEPTORS IN THE IMMUNE SYSTEM BY IN SITU HYBRIDIZATION

The evidence for opiate modulation of the immune system is convincing and raises the issue as to which receptors may transduce these activities. Cloning of the μ, δ and κ opioid receptors has provided the molecular probes to analyze these receptors in different cells of the immune system. Kappa opioid receptor transcripts and binding have been demonstrated in cell lines, however, analysis of circulating populations of immune cells has proven difficult. RT-PCR strategies have been successful in the detection of opioid receptor transcripts in immune cells (Gaveriaux-Ruff *et al.,* 1994; Chuang *et al.,* 1994, 1995; Sedqi *et al.,* 1995; Sharp *et al.,* this volume).

In collaboration with Karen Miotto, we have used PCR to analyze mixed populations of human immune cells and have obtained positive signals for μ, δ and κ receptors yet analysis by Northern blots has not revealed bands. However, strong bands on Northern blots were observed in RNA extracts from a number of different immune tissues with a probe for the orphan receptor ORL-1 which is highly homologous to opioid receptors. We have begun to approach analysis of opioid receptors in the immune system by in situ hybridization which should be capable of detection of rare cells expressing opioid receptors. Human lymph nodes have been sectioned and probed with riboprobes generated from fragments of the human μ, δ and κ genes. Scattered cells were observed with all three probes in a population of T or B cells outside of the germinal centers. Studies are currently in progress to fully characterize these immune cells. (Supported by USPHS grant DA05010 from the National Institute on Drug Abuse and the Norman Cousins UCLA PNI Program)

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DRUG TESTING IN THE WORKPLACE: LEGAL, TECHNICAL AND SCIENTIFIC ISSUES

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Drug testing, its legality, technology, and utility, has been and continues to be debated. While there is little disagreement that under certain circumstances, drug testing has been found 10 be legal, there is less agreement about how and to what ends it is used.

The technology for testing biological specimens for drug and metabolites is becoming ever more sophisticated, that is, sensitive and specific. There is a double-edged sword, in that it portends greater intrusions on individuals, but also is likely lo improve the accuracy and, perhaps more importantly, the ability of drug tests lo measure impairment.

From a research perspective, there remain huge gaps in our knowledge about the effectiveness of testing programs as a deterrent or as a tool in the early identification of addicts. There are also questions about the appropriate responses lo positive tests. While many businesses are referring those who test positive to drug abuse treatment programs, it is important to realize that drug addiction does not equate with drug use, and programs must match their clients to the appropriate level of intervention.

Drug testing is widespread, estimates as high as 30 million tests per year are conducted on American workers. Clearly, this is an example of a "public health" intervention which has been widely adopted without the benefit of a broad science base. Just as clearly, the responsibility lies with the science and research community to provide the science base for maximizing its utility within legal and ethical constraints.

The purpose of this symposium was to review the current laws and policies governing drug testing, its current status in the courts, studies on the effectiveness of such programs, and recent technological developments. A panel composed of legal experts, forensic toxicologists and policy experts discussed these issues.

TECHNOLOGICAL DEVELOPMENTS IN DRUG TESTING

Traditionally, the most objective criteria available for identifying drug use is urine testing. Qualitative urinalysis (positive/negative drug use) is the most widely used technique and provides an objective measure of determining whether recent drug use has occurred over the last two lo four days. Recently, interest has grown in improving urinalysis techniques and adopting other biological fluids and tissues, such as saliva, sweat and hair, that may reveal additional information about an individual's drug use patterns. Quantitative urine testing can improve the usefulness of urinalysis by allowing intra- and inter-group comparisons of frequency and extent to drug use.

Saliva testing, in comparison to urinalysis, offers different information regarding recency of drug use. The detection times for drugs in saliva is similar to that for blood (4-24 hours). Consequently, saliva testing offers the possibility of revealing current drug use that affects an individual's performance in complex psychomotor tasks, such as driving and operating heavy equipment.

Sweat testing has recently become feasable through the development of a new sweat patch device designed to collect non-volatile drugs of abuse from human skin. The device is applied like a Band-Aid to the skin. Substances with the volatility of water or greater leave the device through a membrane barrier. Non-volatile substances are concentrated on an absorption pad inside the patch. Subjects can wear the patch for periods up to several weeks, followed by removal, storage and analysis of the contents of the absorption pad. Preliminary

studies with the sweat patch indicate that it may be useful for detection of single and multiple drug uses over a period of one to four weeks. Currently, its usefulness as a quantitative measure of drug use is being evaluated.

Hair testing appears lo offer thc possibility of monitoring drug use over an extended period of time that is dependent upon the length of an individuals hair. Drugs are scqucstered in air and remain semi-permanently bound for the life of the hair. Since hair grows at an average rate of 1.0-1.5 centimeters per month, analysis of segments of hair for drug content could possibly reveal historical drug use dating back months to years. Some caution is necessary in interpretation of positive hair tests results, however, since environmental contamination of hair can occur. The technology, and scientific knowledge base of each of these new biological measures are improving rapidly. Each technique offers different information regarding the extent, frequency and impact of drug use in selected populations.

LEGAL STATUS OF DRUG TESTING

There is a very important legal distinction between Federal Government, or Federal Government-mandated drug testing programs and private sector initialed drug testing programs. Government employment and private employment extensively regulated by the Federal Government, are protected by the Fourth Amendment to the United States Constitution, which provides that the "right of the people to be secure in the persons *** against unreasonable searches and seizures shall not be violated ****".

The Supreme Court of the United States in Skinner v. Railway Labor Executives Association, 489 U.S. 602 (1989) held that federally required drug testing involving urinalysis is a search to which the Fourth amendment applies. The Skinner case involved the Federal Railroad Administration regulations requiring blood, breath and urine tests of privately employed railroad personnel involved in major train wrecks or who violate certain safety rules. The court noted that certain railway employees discharge duties fraught with risk of injury to others which could result from even a momentary lapse of attention. For this reason the government interest in random testing sufficiently outweighed the employees expectation of privacy. For these and additional reasons the search was held to be reasonable.

In another case, National Treasury Employces Union v. Von Raab, 489 U. S. 656 (1989), the Supreme Court upheld a urine drug testing program not requiring either probable cause or an individualized suspicion of drug use for prospective customs agents; 1) directly involved in drug interdiction; 2) who, if appointed, would carry firearms. Positive test results could be used to preclude appointment to the covered position but not for criminal prosecution.

Most Federal employees, and private sector employees in occupations affected by Federal regulation, are not in such sensitive positions as are transportation employees and customs agents. Consequently, they can only be required to submit to drug testing if there is a reasonable basis to conclude that they have used drugs. However, many categories of employees, both governmental and private, are subject lo random testing: such as employees of nuclear power plants, certain bus and truck drivers, airline flight crews and air traffic controllers.

The private sector legal framework is significantly different because the Fourth Amendment prohibits against "unreasonable searches and seizures" restricts the government--not private employers. Though, as has been noted, extensive government "participation" or "sovereign compulsion" can bring the Fourth amendment protections into play with respect to targeted categories of private employees.

RESEARCH ON DRUG TESTING IN THE WORKPLACE

In 1994, the National Research Council/Institute of Medicine conducted a study on drug use by the American workforce. The subsequent report addressed four primary substantive areas: epidemiology, assessment methods, impact of use on behavior, and effectiveness of drug testing programs. First, based on the epidemiological data reviewed by the committee, the dimension of the problem in terms of severity and magnitude was described. Second, detection and assessment methods currently used in the workplace to detect individual drug use were described. Third, the impact of drug use on behavior will be addressed by examining findings from both laboratory and field studies. Finally, a critical review of the research literature on the effectiveness of workplace drug testing programs was conducted. Empirical evidence pertaining to pre-employment, for-cause, and random drug-testing programs was also discussed, as were studies that have estimated the cost effectiveness of such programs. Within each of these four substantive areas, key committee conclusions and recommendations were presented.

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FUNCTIONAL EVIDENCE FOR EFFECTS OF DRUGS OF ABUSE ON INFECTION AND IMMUNE RESPONSES

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Introductory remarks were given by Dr. Haverkos of the NIDA. He emphasized the importance of continuing study on the relationship between drug abuse, immune response and infection, especially HIV infection and AIDS. In 1994, AIDS was the leading cause of death for American adults aged 25-44 years, and there was a high frequency of AIDS among injecting drug abusers, homosexual/bisexual men, and prostitutes, who reported abuse of huge quantities of alcohol and drugs before developing AIDS. In addition to transmission of HIV infection via injections, several basic scientists in this symposium demonstrated that drugs of abuse can lead to immune dysfunction independent of HIV infections. The impact of continued drug use and related immune dysfunction on HIV disease progression, paradoxically, has not yet been demonstrated in large scale cohort studies of active drug abusers. Further research on effects of drugs on immune function and the implications for HIV infection and disease progression is clearly warranted by these findings.

Dr. Friedman presented results demonstrating the ability of tetrahydrocannabinol (THC) to sensitize mice to infection with *Legionella pneumophila,* an opportunistic intracellular bacterial pathogen which presents as pneumonia and infects macrophages while limiting other aspects of cellular immune function involving T-cells. Mice infected with a sublethal dose of *Legionella* resist challenge with an otherwise lethal concentration of bacteria, 3-4 weeks later. When the major psychoactive component of marijuana, THC, was given simultaneously with a sublethal dose of *Legionella,* the course of subclinical infection was unaltered. However, animals treated in this way were unable to mount a protective immunity against subsequent challenge with lethal doses of *Legionella* Animals that received THC twice, the day of sublethal challenge with bacteria and one day later, at non-toxic doses resulting in blood levels similar to that seen in humans who smoke 1-2 marijuana cigarettes, died within 24 hr from a toxic shock-like syndrome. Mice given only a single dose of THC the day before or after the infectious challenge, however, showed no signs of illness. The toxic shock death was associated with heightened levels of pro-inflammatory cytokines IL1 and IL6. This evidence of loss of immune response to infection and of toxic shock-like death indicate that individuals infected with a common opportunistic pathogen like *Legionella,* who use a drug of abuse like marijuana, may develop potential detrimental effects due to the combined consequences of infection and use of what is widely considered a non-toxic illicit drug.

Dr. Peterson presented data regarding the effects of opiates on glial cells and HIV-l infection as an *in vitro* model of the pathogenesis of AIDS dementia which is known to involve microglial cells, the site of HIV-1 replication in the brain, and cytokines, such as tumor necrosis factor (TNF)-α. Based on previous studies of the potentiating effects of morphine on HIV-1 replication in human peripheral blood mononuclear cell cocultures, the Peterson laboratory tested the hypothesis that morphine would augment viral expression in cocultures of human fetal brain and chronically HIV-1-infected promonocytes (U1 cells). In this *in vitro* model of HIV-l brain infection, morphine was found to enhance upregulation of HIV-1 expression. The mechanism of morphine's proviral activity appeared to involve opiate receptors and an increased release of TNF-α from microglial cells interspersed within the brain cell cultures. The endogenous opioid, dynorphin, a #-receptor agonist, caused similar enhancing effects as morphine. Recently, human microglial cells have been shown to constituitively express κ- opioid receptors, and the effect of activation of these receptors by κ ligands on HIV-1 expression is currently being explored. The results of these *in vitro* studies suggest that opioids may have an immunoregulatory role within the CNS and that pharmacological exploitation of the microglial cell opioid receptor system could lead to new therapies of CNS infections.

Dr. Eisenstein reported on the ability of morphine to sensitize mice to bacterial infection with *Listeria monocytogenes,* a bacterium which replicates in macrophages, and for which activated macrophages represent the major host defense mechanism. Mice innoculated 48 hrs after implantation of morphine pellets with a sublethal dose of *Listeria were markedly* sensitized to infection of the bacteria so that 17 of 18 died. The effect was almost completely blocked by simultaneous implantation of a pellet of the opiate antagonist, naloxone. No animals died when given placebo or naloxone pellets alone. Morphine-pelleted mice also had 200-fold greater *Listeria* burden in their livers 42 hrs post-infection, relative to all other groups. To examine the phagocytic capacity of individual macrophages, the ability to ingest another facultative intracellular bacterium,

Rhodoccus equi, was assessed. *Rhodococcus* is an opportunistic pathogen in AIDS patients. Macrophages from morphine-pelleted mice had enhanced phagocytosis of *Rhodococcus.* As *Rhodoccus* is internalized by complement receptor type 3, the results suggest that the receptor is upregulated in animals given morphine. In another line of investigation, it was observed that peritoneal exudates, as well as spleens and livers, of morphine-pelleted mice were contaminated with *Proteus mirabilis* and *Escherichia coli.* Organ homogenates from controls also contained bacteria; but fewer animals were colonized, the microbial burdens were significantly lower on average, and the organisms were mostly Gram+, not Gram -. Mice pelleted with morphine, but not morphine plus naloxone, were sensitized to a sublethal dose of lipopollysaccharide (LPS), and produced twice as much TNF as controls. These observations are consistent with induction of a septic syndrome by morphine. Release of endogenous LPS from enteric bacteria escaping from the intestinal tract could be responsible for upregulating the capacity of macrophages in the peritoneal cavity to internalize *Rhodoccoccus.* The role of morphine-induced release of endogenous flora in sensitization to *Listeria* infection *in vivo* is still to be assessed.

Dr. Molitor described a swine model of chronic opiate dependency that has been used to characterize long-term effects of exposure to morphine on primary infection of swine with the swine herpes virus (SHV-1) and on secondary infection with *Pasturella multocida,* the most common secondary respiratory infection in swine. Remarkably, swine exposed to SHV-1 showed reduced neural pathogenicity and were protected against the normally lethal neuropathogenic consequences of this virus. On the other hand, morphine caused increased incidence of virally-induced pneumonias compared with control animals infected with SHV-1. Seven days after challenge with SHV-1, and 14 days after initiation of morphine injections, a separate group of animals were challenged with Pasteurella. Compared with controls that did not receive morphine, the morphine-treated animals showed a rapid, severe progression of secondary Pasteurella-induced pneumonia. Systematic examination of the progression of bacterial pneumonia, including analyses of lung pathology for shifts in macrophage populations caused by morphine exposure. Mature forms were depressed in number and recruitment of immature forms was attenuated. Macrophages from these animals also showed impaired response to LPS in regard to their synthesis of IL-1. Also, serum iron levels were greater in morphine-treated swine and zinc levels were lower. Thus, morphine exposure alters macrophage constituency of the lung in both number, type, and function in a way that makes swine more susceptible to the pneumopathological sequelae of SHV- and *P. multocida,* as an apparent effect of the anti-inflammatory properties of opiates in the swine.

Dr. Ronald Chuang presented work concerning the ability of morphine to advance progression of simian AIDS caused by the immunodeficiency virus $SIVmac_{239}$. This monkey model is particularly relevant to attempts to determine the role of opiates in AIDS since it represents the only controllable model of HIV infection that consistently generates highly relevant information for the development of therapies and treatments for HIV infection. The evidence presented indicated that morphine injections enhanced pathogenesis associated with SIV infection relative to SIV-infected monkeys that received saline. SIV viremia was significantly greater throughout the study. At 17 mo after initialion of infection, secondary infections and diseases like giardiasis, enterocolitis, amyloidosis, cholecystitis and lymphoma were more apparent in opiate-treated monkeys than in controls. Morphine-exposed monkeys also showed a significant increase in the mutation rate of SIV which resulted in viral mutants that gave false negative results when assayed with conventional serological screens like ELISAs and western blots. In addition, these viral mutants were shown to be AZT-resistant strains. These findings have important HIV carriers, to supplying evidence that suggest that these retroviruses can mutate into AZT-resistant strains upon opioid treatment even without exposure to AT. Molecular findings were also reported which indicated that κ– and δ–like opiate receptors are present on cells of the immune system. These data are providing valuable insight into the possible mechanisms behind the SIV-modulating properties of opiates.

Concluding remarks of Dr. Donahoe aimed at summarizing the impact of the studies presented. The data presented in this symposium, along with other published reports, make it clear that opiates and THC modulate immune function in a way that can alter host susceptibility to disease. These effects are consistent across models for bacterial and fungal diseases, but appear to be more conditional as regards viral infections. Thus, opiate exposure can have protective effects against viral infection as reported by Molitor for herpes virus of swine, as well as reports from the Donohoe laboratory regarding $SIVsmm_9$; and a laboratory in France regarding infection in mice with Friend leukemia virus **(Veyries *et al.,* JPET 272:498, 1995);** and it can be exacerbatory as reported for $SIVmac_{239}$, by Chuang in this symposium. This conditionality of effect may

relate to variances in the ability of different opiate-dosing regimens to maintain homeostasis between these different studies as well as variances in the pathogenicity and virulence of the viruses used.

Thus, withdrawal from opiate may create conditions that are disruptive to host protection while well-maintained dependencies favor protection, if the virulence of the infecting agent is low enough as not to overwhelm host defenses. Analogies between these hypothetical constructs and the current clinical and social experience with opiate use and abuse were discussed as potential factors that could influence progression of AIDS as well as the ability of epidemiological assessments to monitor such progression in human addicts. There was a consensus that treatment of street addiction to stabilize addicts who notoriously cycle their use of opiates and other drugs is a very important public health and therapeutic objective because of its potential to intervene in the continuing spread of AIDS and other infections by this cohort group.

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SEX, DRUGS, AND COMPULSIVITY: HIV RISK AND MEDICATION TRIALS

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For chemically dependent patients participating in clinical medication trials, factors such as intravenous drug use, sex with IV drug users, and increased unprotected sexual activity (both heterosexual and homosexual) all pose an increased risk for infection with HIV. Numerous issues face researchers who intend to conduct hypothesis-driven research on HIV risk behaviors in the context of medication protocols designed to treat substance abuse. Knowledge of subject characteristics and relevant selection factors is required to generate reasonable hypotheses that can be tested, and to judge the extent to which results in study populations can be generalized. Relevant basic data include: geographical epidemiology; local drug economy; socioeconomic status of the population and subject sample; cultural and racial factors; gender issues; drug preferences and routes of administration; and clinical signs and symptoms and their course.

National statistics from the Center for Disease Control may differ from patient populations treated in particular clinical settings in which substance abuse medication research is conducted. For example, the prevalence of HIV and AIDS cases within the Department of Veterans Affairs is markedly below national figures, although the number of yearly cases treated rose steadily between 1988 and 1994 (from 4,919 to 17,268 cases, respectively). Forty-six percent of those Veterans reported previous homosexual or bisexual behavior, 29% were intravenous drug users, and in almost 13% the risk factor was unknown. Only 3% of the cases identified the risk factor as heterosexual contact.

A five year, NIDA-sponsored study sought to reduce HIV risk behaviors in 426 male Veteran intravenous drug users (IVDUs) in treatment at a Chicago VA Medical Center (Schaefer et al., 1995). Among these Veterans, intravenous drug use within the prior year included cocaine (91%); heroin (78%); or other narcotic substances (27%). The mean frequency of intravenous drug use during a typical month of use was higher for cocaine (77) compared to heroin (33). Eighty-one percent admitted to sharing needles/works, while 12% had frequented a shooting gallery. Eighty-one percent reported never using condoms, and subjects reported an average of 4.2 sexual acts within the last month. While 30% reported trading sex for money, nevertheless only one subject admitted to sexual contact with a male partner. The behavioral complexion of this sample, as well as that described for the VA HIV/AIDS population at large, may be idiosyncratic for Veterans in treatment for HIV/AIDS and/or substance abuse, and may not correspond to substance abusing populations studied in any particular medication trial.

At VA Medical Center-West Los Angeles, 57% of 27 male crack cocaine-dependent, non-IV using treatment seeking Veterans reported an association between cocaine use and a variety of sexual behaviors or fantasies, including continuous/frequent intercourse (60%), use of prostitutes (48%), continuous/frequent masturbation (40%), pornography (32%), voyeurism (16%), exhibitionism (8%), and pedophilia (4%) (Beckson *et. al.,* 1995). Of these, 77% reported little or no distress over these sexual activities and 56% reported no resistance to them. Forty-four percent had not experienced these prior to their cocaine career and 32% reported doing so only while high on cocaine. The 43% whose sexual behaviors started prior to their cocaine addiction reported an increased frequency since using. During periods of abstinence from cocaine, 33% did not experience their characteristic sexual behaviors or fantasies, and of those who did, 64% did so less frequently. Forty-seven percent reported that their sexual fantasies or behaviors had precipated relapse to cocaine use, and 54% reported that cocaine use precipitated recurrence of sexual behaviors or fantasies. Thus, the association of characteristic sexual behaviors or fantasies with crack cocaine use is common among male crack addicts, causes little or no subjective distress, and leads back to cocaine relapse while cocaine reciprocally leads to sexual behaviors.

The connection between crack cocaine and sexual activity has been noted and postulated to reflect the particular properties of crack, however, the nature of the clinical syndrome remains controversial. One perspective is that sexual "addiction" and drug addiction are two distinct behavioral disorders, and that patients may suffer from "dual diagnoses" of both (Carnes, 1994). Sexual addiction has been operationalized using modification of the diagnostic criteria for substance dependence, including loss of

control and continued behavior despite adverse consequences. Sexual addiction/compulsivity may persist despite abstinence from alcohol and drugs, and may lead the sufferer back to chemical use. Another proposal postulates an "obsessive-compulsive spectrum" of disorders involving loss of control over intrusive thoughts, impulses, and behaviors. In this model, sexual compulsivity and drug addiction are on a continuum of impulse control disorders, along with compulsive gambling, trichotillomania, obsessive-compulsive disorder, etc. The behaviors and impulses may be relatively pleasurable or distressing. Dysregulation of serotonergic neurotransmission is hypothesized to underlie these disorders. The neurotoxicity theory of substance dependence postulates that substance-induced increases of dopamine metabolism in vital pleasure and reward brain pathways create damaging free radicals that permanently alter the functioning of these systems (Bartzokis *et al.,* 1995). Neuroanatomical components of these systems include the basal ganglia and frontal lobes, which are critical for behavioral programming and have been demonstrated to be dysfunctional in Obsessive-Compulsive Disorder (DSM-IV criteria). Therefore, there is a predicted association of substance dependence with other disorders involving pathological motor and cognitive programming, such as sexual compulsivity.

HIV risk behaviors may reflect the sociocultural context as much as specific drug of choice or route of administration. Urban female crack cocaine addicts commonly obtain their drugs through prostitution and exchange of sex for drugs, and cocaine use in crack house settings often includes such exchanges. Thus, sexual behavior is readily available and may be more opportunistic than compulsive in these settings. Ethnographers have documented that the women engaging in these exchanges commonly are of poor, minority background; have experienced childhood exposure to alcohol, drugs, domestic violence, sexual and physical abuse; and have low self-esteem. Their drug craving puts them in a weak position; sexual degradation, violence, and aggression commonly accompany sex-for-crack exchanges. However, these may be a "contemporary public idiom for poverty, ethnic segregation, and polarized gender relationships" (Bourgois and Dunlop, 1993). The "demonization of the pharmacological properties of crack" is cautioned against. Sexual drive and fantasies 'are a sociobiological given, and the linking of sex and cocaine via classical conditioning creates a powerful menu of internal and external triggers for relapse to cocaine use. "Readiness for change" has been postulated as an important variable for treatment outcome in substance use disorders (Prochaska *et al..,* 1992). Treatment seeking drug addicts may not accept or incorporate risk behavior interventions, as their readiness for change may not extend to their sexual behaviors.

HIV testing in clinical medication trials may pose problems for the conduct and success of the trial, For example, subjects may refuse to participate if HIV testing is mandatory because of fear of testing positive, fear of breaches of confidentiality, etc. Patients who are tested and are discovered to be positive may, if told the results, become acutely distressed and drop out of the study, or become suicidaI and need to be terminated. The stress of being tested or testing positive may have significant effect on measures of emotion, physical complaints, drug craving, and drug use. The medication being evaluated for the treatment of drug dependence may be less efficacious in a neurochemical milieu of extreme distress. In addition, the incorporation of significant HIV prevention and/or behavioral inlervention into a clinical trial protocol might increase the effective intensity of psychosocial intervention where low intensity intervention had been desired. This could then result in "wash-out" of medication effect in the trial, particularly with the small lo medium effect sizes expected of medications used to treat substance use disorders.

It is often stated that treating drug abuse will induce HIV risk behaviors, however, sexual behaviors may actually increase for a variety of reasons. For example, patients may feel better once their cocaine addiction is in remission, they may have improved potency to perform sexually and they may be more sociable as a result of a reduction in paranoia and social isolation, as well as improved socio-economic functioning. Substitution of one compulsive behavior for another may occur, with increased sexually compulsive behaviors during periods of chemical abstinence. Cocaine withdrawal dysphoria and anhedonia may stimulate craving for sexual gratificalion. Abstinence from cocaine may result in increases in other substance use (*e.g.,* alcohol) which in turn may be sexually disinhibiting, leading to HIV risk behaviors. Modification of HIV risk may be thought to have a positive impact on substance use, however, harm reduction strategies seeking to reduce morbidity by substitution of clean needles might reduce the inhibiting fear of contracting HIV, especially by intravenous roule. Condom use may increase confidence about remaining HIV-negative, thereby removing the inhibition to engage in sexual situations that may trigger relapse to drug use. HIV education itself may not result in true harm reduction through changes in actual

sexual practices. Addicts may harbor the unrealistic belief that condom use provides invulnerability to HIV, and consequently may have more partners, more sex acts, etc. This may be combined with poor condom use technique, inconsistent use of condoms, or omission of condom use for non-intercourse acts which are believed to be "safe". All of these may lead to an increased risk of HIV transmission.

It is often assumed that patients truthfully report sexual behaviors, however high-risk homosexual encounters may be concealed. Reliance on subjects' self-reports may not be accurate, requiring the use of collated sources of history or reliance on direct community observation. Ethnographers report that despite awareness of HIV and claims by cocaine addicts that they exclusively use condoms; direct observation shows otherwise. Condoms are rarely found in crack houses where sex-for-cocaine exchanges occur. Money is usually spent on crack, not condoms. Use of condoms is omitted often based on the nature of the sexual relationships, the stale of intoxication, availability of condoms, etc. Cocaine-craving women and men in sex-for-crack exchanges are usually not in the position to insist on the use of condoms by the men who possess cocaine. Another potential pitfall of addressing HIV in clinical trials can include impaired drug abuse counseling as a result of staff biases, fear of contagion, moral disapproval, etc. In the course of data management, HIV results may be improperly disclosed. If HIV status is determined to be positive in the course of a clinical trial, what additional tests or interventions are scientifically, medically, and/or ethically indicated during the course of the trial'? If a subject in such a trial is immune-deficient, does this affect decisions regarding treatment with medication that may have unknown effects on the human immune system?

To conclude, as HIV becomes more prevalent among substance abusers, clinical trials designed to develop more effective treatment for drug dependence will increasingly encounter subjects with high risk behaviors or HIV infection. This provides a challenge and an opportunity to study interactions between drug use and high risk behaviors; effects of drug abuse treatment on risk behaviors and on the health of HIV-positive subjects; and the effects of risk behaviors and HIV disease on medication pharmacokinetics and efficacy. Knowledge of epidemiological, behavioral, and cultural phenomena surrounding sex-drug interactions, and understanding of melhodological and design issues, are necessary for the development of well designed, hypothesis-driven research on HIV in drug dependent clinical trials subjects.

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NEUROENDOCRINE FUNCTION AND THE RELATIONSHIP TO ADDICTIONS

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Role of Steroids in the Acute and Chronic Effects of Drugs of Abuse. All psychoactive drugs affect the secretion of steroids in rodents, non-human primates and humans. Potent effects are exerted on both the hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-gonadal axis. In fact, this effect is so predictable and robust that one can use drug-induced changes in steroid levels to predict the potency and potential abuse liability of substances of abuse. Although many investigators continue to carry out very important studies of the mechanisms underlying the effects of substances of abuse on endocrine function, a potentially more important issue is whether these drug-induced changes in steroid levels may mediate the acute and chronic effects of substances with significant abuse potential. A great deal of evidence is accumulating which suggests that this hypothesis may be correct, but at the present time it is surprising how little rigorous effort has been expended to examine this important problem. There are several strategies which have been used to assess whether steroids influence the pharmacology of substances with significant abuse potential: sex differences; removal (castration) or addition of steroids; and puberty-retated changes in the sensitivity to abused, psychoactive compounds. The data, which can most appropriate be classfied as preliminary at this time, can be summarized as follows.

Data are rapidly accumulating to suggest that the acute effects of morphine and cocaine are markedly different in male and females which cannot be attributed to pharmacokinetic differences. Importantly, masculinization of females or feminization of males reverses these sex-related differences. There are also several preliminary reports that the reinforcing properties of drugs are quantitatively different in males and females. In addition to these sex-related differences, castration of males and females for relatively brief periods of lime has been shown to markedly after the response to psychoactive drugs when compound to intact animals. It has been shown that the acute effects of opiates and the development and expression of tolerance and physical dependence are markedly different in pre-pubescent male and female rats when compound to adults and that, with the onset of puberty, adult-appropriatc responses quickly develop suggesting that steroids may influence these processes.

A good deal of data now suggests that drug-induced changes in steroid levels may be involved in the acute and chronic effects of many substances of abuse. While there appears to be a wide range of data with regard to this important topic, it must be acknowledged that the efforts to examine this issue have been non-systematic, and not nearly as intensive as they should be. Many issues remain to be examined. For example, many more definitive pre-clinical studies are badly needed to further examine the role of steroids in the reinforcing properties of drugs and the development and expression of tolerance and withdrawal. On the basis of many pre-clinical observations, several questions should be rigorously assessed in humans, which quite surprisingly have been largely ignored: (a) are the sex-related differences in the acute effects of abused substances: (b) are their reinforcing properties of abused substances quantitiably different in males and females; (c) do tolerance and physical dependence show sex-related differences; and (d) are there sex-related differences in treatment outcome and drug prevention strategies?

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Effects of Addictive Drugs on Neuroendocrine Function in Development. The purpose of this presentation was to address the reciprocal relationship between drugs of abusc and endocrine function during development. The talk addressed the treatment parameters which influence what the endocrine consequences of drug exposure are, and described the spectrum of endocrine disorders that have been described. The mechanism of drug action (*i.e.,* stimulation of opiate receptors, inhibition of monoamine uptake, etc.) and window of exposure were discussed as primary determinants of drug actions, with a lesser but important role played by the development of tolerance and sensitization, and materna1 physiology. Three types of endocrine consequences were described. The first of these was the production of a transient change in hormone production that then caused reversible changes best described as developmental delays. The inhibition of LH secretion and delay of pubertal development in female rats was discussed as an example of this problem. Such effects have been described following administration of both opiates and cannabinoids. Next, the ability of transient changes in hormone secretion to produce permanent effects on the development of hormone-dependent systems was described. This

is probably the most serious of the endocrine consequences, as a brief exposure can produce a permanent effect. The suppression of thyroid hormone production by opiates and the absolute dependence of CNS maturation on appropriate thyroid hormone levels during critical developmental windows was cited as an example. The classic work of Altman describing the dependence of cerebellar development on thyroid hormone levels was reviewed. The final consequence considered was the ability of transient changes in hormone secretion to produce permanent changes in neuronal sensitivity by phenomena similar to those described in adults. The ability of cocaine to stimulate the HPA axis, and the possible role of both CRF and the adrenal glucocorticoids cortocosterone to produce such changes in rats was used as an example. Developmental increases in cocaine-induced HPA secretion were described which correlated with a gradual increase in capacity to achieve sensitization to the locomotor stimulant properties of cocaine. This example provided an example of a situation in which the developing animal was relatively protected rather than vulnerable to a chronic drug effect. In summary, this presentation demonstrated that hormone secretion elicited by drugs of abuse during development have potential for many outcomes in the fetus. The most concerning of these is perturbation in levels of hormones during critical periods for the development of hormone-sensitive organs like the brain. However, the presentation also demonstrated that the developing animal can be either more vulnerable, or relatively protected, in comparison to adult animals, depending upon the critical issue of the window of developmental exposure to the drugs.

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Impact of Opiate and Cocaine Addiction on the Stress Responsive Hypothalamic-Pituitary-Adrenal Axis and Prolactin Release in Humans. Studies from our laboratory as well as from others have shown that both opiate addiction and cocaine addiction have profound impact on the stress responsive hypothalamic-pituitary-adrenal axis in humans with addictive diseases. Also, studies have shown that prolactin release is altered in the setting of both opiate addiction and cocaine dependency. We have hypothesized that altered responsibility to stress and stressors contributes to the development and perpetuation of each of three major addictive diseases: opiate addiction, cocaine dependency and alcoholism. Studies in our laboratory, including both pre-clinical studies using *in vitro* systems and animal models, at the molecular, neurochemical and behavioral level, as well as our basic clinical research studies, have addressed the possible role of the endogenous opioid system in each of these addictive diseases, as well as the role of the mesolimbic-mesocortical, nigrostriatal and the tubero-infundibular dopaminergic systems, and the interaction between the endogenous opioid system and the dopaminergic systems.

For many of the molecular studies in our laboratory, we have utilized a modified solution hybridization RNAse protection assay. With this assay, using probes resulting from recent cloning of the endogenous opioid receptor genes by several groups, we have been able to remap the brain with respect to the presence, absolute and relative amounts of mRNAs of each of the endogenous opioid receptors and their ligands, that is, the genes for preprodynorphin, preproenkephalin and pro-opiomelancortin. Our findings have confirmed and extended findings from other laboratories using other technologies. Of special interest has been the finding of abundant mu and kappa opioid receptor gene expression, as well as abundant amounts of preprodynorphin and preproenkeplin mRNAs in all regions of the mesolimbic, mesocortical and nigrostraital dopaminergic systems, as well as in the hypothalamus. Using these techniques we have also extended earlier studies by measuring levels of CRF and mRNA, the hypothalamic peptide corticotropin releasing factor which is one of the major modulators of pro-opiomelancortin gene expression and peptide production. In these studies in which we have been able to extend earlier work by the availability and use of an experimental approach which allows determination of the levels of mRNAs from several genes of interest in specific brain and pituitary regions from single animals, we have been able to quantitate the effects of dexamethasone on suppression of CRF mRNA and POMC mRNA, as well as the effects of CRH on enhancing POMC mRNA. Further studies are in progress to determine the effects of opioids which, in humans, are short-acting (*e.g.,* heroin and morphine) and also long-acting (*e.g.,* methadone and LAAM which must be administered by steady-state infusion by pump in rodents to achieve a pharmacokinetic profile similar to that seen in humans).

In studies to date we have found that, in parallel with our studies in humans maintained on methadone for treatment of opiate addiction, methadone delivered by pump in rodent has no effect on the mRNA levels for CRH or POMC, and no effects on mu opioid receptor gene expression. We have found that during cycles of heroin addiction, there is a hypo-responsivity to stressors and during long-term methadone maintenance, there is a normal responsivity to stress and stressors. In contrast, we have reported an atypical hyper-responsivity to stress in opiate-free, former opiate-dependent individuals. We have hypothesized that this atypical responsivity

to stress and stressors may contribute to or cause drug hunger or craving and thus the relapse to illicit use of opiate drugs. In recent and ongoing studies we have found that in recently abstinent cocaine addicts, studied in a stress-minimized environment, there is also a hyper-responsivity to a chemically induced stressor, similar to that previously observed by our group in medication or drug-free former opiate-dependent persons.
Other recent studies from a variety of groups have supported this hypothesis of an increased self-administration of drugs of abuse, especially stimulants, in animals evidencing heightened response to stressors. In addition to these findings, several groups have found that prolactin release is abnormal in some recently abstinent cocaine addicts. The findings support the findings of our laboratory microdialysis studies, in which significantly lowered dopamine levels are found in the extracellular fluid of both the caudate putamen and in the nucleus accumbens of animals who have received two weeks of "binge pattern cocaine treatment. It is possible than an altered responsivity to dopamine may occur in such it state. Further studies are ongoing to elucidate the effects of chronic cocaine on the tuberoinfundibular dopaminergic system as well as the other dopaminergic systems related to the rewarding effects of drugs of abuse. At the same time and in parallel, studies of the effects of the drugs of abuse on the endogenous opioid system continue.

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The Effects of Chronic Cocaine Self-Administration on the Menstrual Cycle in Female rhesus Monkeys
The effect of chronic cocaine self-administration on menstrual cycle duration and anterior pituitary and gonadal hormones were examined in adult rhesus females (Macaca mulatta) for periods of two to three years. Drug naive females were adapted to the laboratory until stable ovulatory menstrual cycles occurred and then implanted with intravenous catheters and trained to self-administer cocaine and food on a simple operant task during four daily sessions. Each monkey could control the frequency and amount of cocaine injected up to a limit of 8 mg/kg/day. Cocaine intake averaged 5.95 (± 0.40) mg/kg/day. Under these limited cocaine access conditions, monkeys remained healthy and active and food intake and body weights were normal. Thus far, the effects of chronic cocaine self-administration on menstrual cycle duration have been examined for 181 menslrual cycles and approximately one-half of all cycles were of abnormal duration. Short cycles consistent with luteal phase defects accounted for one-third of the abnormal cycles. The remainder of the abnormal cycles were amenorrheic or one standards deviation longer that the pre-cocaine baseline cycle average. Amenorrhea was defined as cycles lasting 60 days or more without menstruation and amenorrheic cycles of 61 to 190 days were observed during cocaine self-administration. In control monkeys studied for 155 cycles, 94% of the cycles were of normal duration and there were no amenorrheic cycles. These data suggest that chronic cocaine exposure disrupts menstrual cycle regularity in otherwise healthy monkeys studied under controlled conditions. These studies are continuing and analysis of the endocrine characteristics of the menstrual cycle is ongoing. These data are consistent with clinical reports of menstrual cycle abnormalities in cocaine and polydrug abusers.

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Pulsatile Release of Adrenocorticotropin Hormone (ACTH) and Luteinizing Hormone (LH) in Drug Reinforcement. There is increasing evidence that the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis may be involved in the reinforcing effects of opiates, alcohol and cocaine. We have investigated the temporal concordance of salient drug reinforcement effects and the pulsatile release of anterior pituitary hormones in men and women following acute alcohol and cocaine administration. A cluster analysis program was used to characterize ACTH pulses and to quantify pulse frequency and amplitude. These studies were also carried out with new procedures for determining plasma ACTH concentration with radio-immunoassays which have no cross reactivity with other anterior pituitary hormones. Both cocaine and alcohol significantly increased the pulse amplitude of ACTH without modifying pulse frequency. The time course of alcohol and cocaine effects on pulsatile ACTH release are closely correlated with pharmacokinetic parameters of absorption, distribution and elimination of alcohol and cocaine in humans. Cocaine also significantly increases the pulse amplitude of luteinizing hormone in men and women, and this effect occurs promptly following intravenous cocaine administration. The mechanisms underlying both ethanol and cocaine induced effects on the pulsatile release of ACTH and LH involve corticotropin releasing factors (CRF), neuroadrenergic, endogenous opioid peptide and dopaminergic regulatory systems within the brain, particularly in the basal hypothalamus. Data obtained in our studies also indicate that there may be ethnic and gender related differences in cocaine pharmacokinetics, and these differences also modulate cocaine effects on the pulsatile release of anterior pituitary hormones.

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CANNABINOIDS: RECEPTORS, ENDOGENOUS LIGANDS AND A NEWLY SYNTHESIZED ANTAGONIST

F. Barth; R. Mechoulam; E. Fride; S. Deadwyler; and B. Martin

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The symposium dealt with several new issues concerning cannabinoid receptor activation, the existence of an endogenous ligand for the receptor and the most recent discovery of a newly developed antagonist for the cannabinoid receptor.

The first speaker was Dr. Francis Barth from Sanofi Researche in France, on the discovery of the new CB1 cannabinoid receptor antagonist, SR141716. Dr. Barth's talk described several experiments in which the antagonist effectively blocked, in a competitive manner, the actions of either potent synthetic cannabinoid receptor ligands or the endogenous cannabinoid substance amandamide. *In vivo* binding studies showed that the cannabinoid binding sites remained blocked for at least 12 hours after an oral dose of 3 mg/kg. *In vivo* tests included cannabinoid-induced hypothermia, ring-immobility and antinociception (ED50 = 0.11-1.7 mg/kg). *In vitro* studies showed that SR141716 antagonized the inhibitory effects of the cannabinoid agonist CP55940 on adenylyl cyclase in CHO cells expressing human CB1 cannabinoid receptors (IC50 = 6 nM) versus the CB2 receptor (IC50 = 3000 nM). It also antagonized the inhibitory action of cannabinoid agonists (Win 55212-2. CP55940, anandamide) on mouse vas deferens contractions (pA_2 = 8-9) as well as on long-term potentiation in rat hippocampal slices. Interestingly, the effects of SR141716 administered by itself improved short-term olfactory memory situation, as well as increased wakefulness and latency to REM sleep in rats. It is expected that SR141716 will provide a useful tool to study the physiology and pharmacology of cannabinoid receptors and possibly assist in the development of new therapeutic agents acting on the central nervous system.

The second speaker was Dr. Ester Fride from Professor Raphael Mechoulam's laboratory who described the agonist and antagonist properties of endogenous cannabinoids. Since the discovery of the anandamides, endogenous ligands of the CB receptor system, a body of evidence has emerged which suggests a functional role for the amandamides. Professor Mechoulam's research group has shown that anandamide (arachidonyl ethanolamide, 20:4, N-6), when administered *in vivo,* produces similar effects compared to cannabinoids such as Δ^9-THC or Δ^8-THC, in the same dose range (5-100 mg/kg, i.p.). Thus, ambulation, rearing and defecation in an open field are depressed; immobility on a ring is increased; body temperature decreased and the pain threshold increased. However, they have also noted several differences between THC and anandamides. Thus anandamide (20:4, N-6) and especially the more recently discovered endogenous anandamides (22:4, N-6 and 20:3, N-6) display partial agonist characteristics in the above mentioned series of assays.

Second, they have observed that low doses of anandamide (0.01 mg/kg) produce the opposite effects to high doses: hyperlocomotion, increased defecation and a tendency toward hyperaigesia. This effect was much less clear after injection of a low dose of Δ^9-THC compatible with the sporadic observations of stimulatory effects by low doses of cannabinoids 13]. They suggested that the discovery of the anandamides has made it possible for the first time to clearly separate the depressant from the stimulatory effects of cannabinoid receptor ligands.

A third difference between anandamides and THC is the ability of very low doses (0.0001-0.01 mg/kg) of anandamides (20:4, N-6 and 22:6, N-3) to reverse the depressant effect of a high dose of THC in the behavioral assays. Similar observations were made by Z. Vogel and J. Barg at the Weizmann Institute of Science in $N_{18}TG_2$ neuroblastoma cells, where pre-exposure to very low concentrations of anandamides decreased the inhibitory potency of Δ^9-THC on forskolin-stimulated adenylate cyclase activity. In contrast, very low concentrations of Δ^9-THC had no inhibitory effects on high doses of THC or anandamides. The latter data may be interpreted in various ways. For example, allosteric binding of the CB receptor or selective activation of Gs proteins by low doses of anandamides as opposed to the well established activation of Gi protein by high doses of CB receptor ligands. Dr. Fride also described the response to THC or anandamide in developing mice for motor activity and pain response on a hot plate. Although a partial effect of Δ^9-THC was observed from day 15, the developing pups did not show a significant response to anandamide until adulthood. This is compatible with the gradual development of CB receptors and with the clinical observation of an absence of cannabimimetic side effects of THC when used as an antiemetic agent in the treatment of juvenile cancer

patients. Furthermore, administration of anandamide (20 mg/kg, *s.c.*) to mice during the last trimester of gestation, produced differences in the tetrad of assays used to assess cannabimimetic effects. Thus, adult offspring displayed lower motor activity and catalepsy on the ring; depressed defecation, hypothermia and analgesia without a cannabimimetic stimulus. On the other hand, when challenged with anandamide or THC, the prenatally exposed offspring responded to a much lesser extent compared to offspring from control mothers. They are currently investigating whether changes in CB receptors is responsible for these behavioral alterations.

The third speaker, Dr. Sam Deadwyler, spoke on several issues concerning the functional significance of cannabinoid receptor occupancy. Initial comments concerned evidence from his and Dr. Steven Childers' laboratory showing that cannahinoid receptor modulation of voltage-dependent potassium channel currents (A current) via CAMP-dependent processes in hippocampal cells in culture, was dependent on several factors including degree of activation of the Gi/o proteins via the cannahinoid receptor. Autoradiographic assessment of this process by Dr. Childers' group has demonstrated that G-protein activation by the receptor and receptor density in different brain regions are not necessarily equivalent. It was also shown that cannabinoid CB1 receptor modulation of voltage-dependent potassium A current was blocked in a dose dependent manner by SR141716, the CB1 cannabinoid receptor antagonist. This was true for WIN 55212-2 and methanandamide stimulation. New evidence was presented supporting the hypothesis that cannabinoid receptor modulation of potassium current was via one of two possible types of identified subtypes of these channels in hippocampal cells in culture. Either the Kvl.4 or Kv4.2 channel subtypes were isolated as possible candidates to mediate the effects of cannahinoids. Finally the effects of cannahinoids on short-term memory measured in a delayed nonmatch-to-sample task were described, showing that the possible underlying mechanism for memory disruption by marijuana could act via cannabinoid receptor activation of voltage-dependent potassium channels on afferents of fibers to the hippocampus from other conical areas. The latter hypothesis is supported by electrophysiological evidence from animals performing the task on drug versus non-drug days.

The fourth speaker was Dr. Billy Martin who also reported on the antagonistic properties of SR141716. This compound was found to be highly effective in blocking the effects of Δ^{9}-THC in several mouse behavioral assays. The AD50 values were less than 1.0 mg/kg, and the antagonism lasted for several hours following i.v. administration. SR 141716 produced slight antagonism of morphine-induced antinociception in mice, but only at doses which were approximately 100 times greater than those necessary for blocking THC's effects. This antagonist also blocked the cue in rats trained to discriminate Δ^{9}-THC. This highly selective and potent antagonist provided Dr. Mario Aceto the opportunity to determine whether it was possible to precipitate a withdrawal syndrome in rats chronically infused with Δ^{9}-THC. In rats continually infused with doses ranging from 12.5 to 100 mg/kg/day during a four-day period, challenge with an i.p. injection of SR 141716 (10 mg/kg) resulted in a unique behavioral syndrome which emerged within 10 min. and lasted for 30-60 min. The most prominent effects were "wet-dog shakes" and facial rubbing which were quantitied. In addition, SR141716 challenge in THC-infused rats resulted in ptosis, backward movements, scratching and tongue rolling. These results are consistent with earlier clinical findings that marijuana is capable of producing dependence as evidenced by physical withdrawal signs. It remains to be established what quantity of marijuana and frequency of exposure are required for producing dependence in humans.

BASIC NEUROBIOLOGY OF ABUSED DRUGS

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This symposium on "The Basic Neurobiology of Abused Drugs" was designed to review general neurobiological concepts relevant to the acute and chronic actions of abused drugs, including opioids, stimulants and sedatives. The four presentations included: 1) An overview of neuroanatomical pathways involved in drug reinforcement, craving and withdrawal; 2) the neurophysiology of dopaminergic neurons and their patterns of activity during exposure to abused drugs; 3) intraneuronal effects on second messenger system as cyclic AMP, and 4) intranuclear gene transcription within neurons during exposure to abused drugs. The final discussion overviewed these layers of intranuclear, intracellular, and intraneuronal events and their relationship to developing new treatment approaches for substance abuse.

George F. Koob - Neural Pathways in the Brain that Mediate Various Behavioral Aspects of Dependence, Including Withdrawal Signs. Drug addiction can be considered in the context of perturbations to the brain systems involved in psychological constructs of reinforcement. The sources of reinforcement in the addiction cycle include the acute positive reinforcing effects of drugs, the negative reinforcement associated with drug abstinence, and conditioned positive and negative reinforcement. Work in our group is focused on identifying brain circuits and neurochemical systems involved in the reinforcement associated with drug dependence. The brain regions of the nucleus accumbens and atnygdala have been identified as important substrates for the reinforcing and dependence producing properties of drugs, and have led to some testable hypotheses regarding the basic neurobiologic nature of drug dependence. Dopamine systems in the region of the nucleus accumbens and amygdala appear to be critical for the acute reinforcing effects of indirect sympathomimetics like cocaine and amphetamine. New data suggest that the dopamine D-1 and dopamine D-3 receptors may be particularly important for the reinforcing effects of cocaine. Opiate receptors in these same regions appear to be critical for the acute reinforcing actions of morphine and heroin. Multiple neurotransmitter systems of the brain reward systems including GABA, glutamate, dopamine, serotonin and opioid peptides appear to be involved in alcohol reinforcement. The opiate receptor subtype important for both the acute reinforcing and dependence-inducing effect of heroin appears to be the mu receptor. Multiple neurotransmitter systems in this same circuitry including GABA, glutamate, dopamine, serotonin and opioid peptides appear to be involved in alcohol reinforcement.

The same basic circuitry appears to have a role in the motivational aspects of drug withdrawal. Brain reward systems that are facilitated by the acute administration of reinforcing drugs such as cocaine show the opposite effect or increases in threshold during cocaine withdrawal. In opiate dependent animals the nucleus accumbens and amygdala appear to be sensitized to the aversive effects of opiate antagonists, and these opiate receptors may be responsible for the aversive stimulus effects associated with opiate abstinence. The brain sites for the physical signs of opiate withdrawal appear to be more widely distributed and include the noradrenegic systems emanating from the locus coeruleus. Dependence on ethanol is also associated with elevations in reaward thresholds that may reflect the aversive motivational state important for maintaining ethanol dependence. Neurochemical systems implicated in such negative motivational states include the same neurochemical systems implicated in the acute reinforcing actions of these drugs, such as the dopamine system and the GABA system. However, ethanol dependence appears 10 recruit neurochemical systems not obviously involved in the acute reinforcing action of these drugs, such as the brain corticotropin releasing factor system.

A body of converging evidence suggests that there are critical common elements within a neuro-anatomical system described as the "extended amygdala" that may be important in mediating both the positive and negative reinforcing components of drug dependence. Animal models for both positive and negative conditioned drug effects are being developed as animal models of "craving" and future studies will be directed at understanding the neurobiological substrates for these conditioned drug effects. These studies not only provide critical information about the neurobiological substrates of drug abuse and dependency, but also about the

neurobiological substrates of the reinforcement mechanisms that are compromised in severe mental disorders such as depression and mania.

Frank White - Neurophysiology of Dopaminergic Neurons. This review of the neurophysiology of dopaminergic neurons began by distinguishing between the burst of regular firing pattern of dopamine neurons. Burst firing causes a marked increase in dopamine release into brain areas such as the nucleus accumbens. This burst firing by neurons in the ventral tegmental area (VTA) can be induced by neurons located in the prefrontal cortex. These prefrontal neurons release excitator amino acids that stimulate AMPA receptors. Bursting is also induced by norepinephrine stimulation of alpha adrenergic receptors from neurons located in the locus coeruleus. Bursting activity is decreased by stimulation of the D2 autoreceptor and by GABA neurons which feed back from the nucleus accumbens to the VTA. Repeated cocaine administration causes an increased sensitivity of the excitatory amino acid pathways from the prefrontal cortex which project onto these dopaminergic cells, thereby increasing bursting activity.

The critical dopaminergic receptor in the nucleus accumbens is the D1 receptor which tends to decrease neuronal activity in the nucleus accumbens. D1 knockoul mice, which lack D1 receptors, show no increase in locomotor activity when they are given acute doses of cocaine. D2 agonists also produce no response in these mice indicating the need for D1 receptor stimulation in order to get the D1 effects on motor activity. The effects of chronic cocaine stimulalion of the D1 receptors is to hyperpolarize the neurons in the nucleus accumbens and, therefore, decrease the probability of action potentials occurring in these neurons. This lowered excitability of these neurons in the nucleus accumbens is mediated by cyclic AMP and phosphokinase A, which lead 10 decreases in the intraneuronal sodium current through sodium ion channels.

Eric Nestler - Adaptations in Intracellular Signaling Pathways as Mediators of Drug Addiction. All drugs of abuse effect the brain initially by influencing the amount of a neurotransmitter present at the synapse or by interacting with specific neurotransmitter receptors. For example, cocaine blocks dopamine uptake and thereby enhances and prolongs the actions of endogenous dopamine, whereas opiates are agonists at opioid receptors. However, despite these initial extracellular actions, the many effects that these drugs exert on the brain are achieved ultimately through perturbations in post receptor, intracellular signal transduction pathways that mediate these extracellular mechanisms. These intracellular pathways involve G proteins, second messengers and protein phosphorylation involves the addition or removal of phosphate groups from specific proteins by protein kinases and protein phosphatases, respectively. Alteratiotions in the phosphorylalion state of a prorein then alters its function. Since virtually all types of neural proteins are regulated by phosphorylation, a drug of abuse, by triggering changes in protein phosphorylation pathways, will eventually influence a wide variety of processes in its target neurons. One hypothesis is that repeated exposure to a drug of abuse would lead to repeated perturbations of these intracellular pathways, which would then trigger adaptations in some of the same signaling proteins that mediate the drug's acute effects. Such adaptations could mediate the phenomena of tolerance, sensitization, and dependence that are often used to characterize a drug addicted state. Evidence to support this hypothesis has been obtained for the nucleus accumbens (NAc). This brain region has been implicated as playing an important role in the reinforcing and locomotor-activating properties of most drugs of abuse. We have found that chronic administration of opiates, cocaine, or alcohol to rats produces an up-regulalion in the cAMP second messenger and protein phosphorylation pathway in the NAc, with reductions in levels of Gi and increases in levels of adenyl cyclase (the enzyme that catalyzes the synthesis of cAMP) and protein kinase A (the type of protein kinase that is activated by cAMP). The adaptations are specific to the NAc, and require chronic administration of the drugs. Moreover, the adaptations are not induced in the NAc in response to several other types of psychotropic drugs (e.g., antidepressant and antipsychotic drugs) that lack reinforcing properties. Studies utilizing the drug self-administration paradigm and tneasure of locomotor activily and sensitization have provided direct evidence that up-regulation of the cAMP pathway represents part of a common molecular mechanism by which opiates, cocaine, and alcohol regulate the mechanisms of drug reinforcement and locomotor activity in the NAc.

Since up-regulation of the cAMP pathway involves altered levels of specific signaling proteins and of their mRNAs, one possibility is that drug regulation of gene expression may be involved. We have, therefore, studied drug regulation of transcription factors as one mechanism that could underlie the chronic actions of

drugs of abuse at the NAc. Transcription factors are proteins that bind to the regulatory regions of certain genes and thereby regulate the rate of their transcription. Interestingly, we have identified novel transcription factors, termed chronic Fras, that are induced following acute drug exposure, but once induced by chronic treatment persist in the brain with a long half-life. We are studying the possibility that induction of the chronic Fras mediates some of the unique long-term effects that cocaine and morphine exert on the NAc. By combining the tools of molecular neurobiology with the more traditional disciplines of neuropharmacology and behavioral neuroscience, it will be possible to build an increasingly more complete understanding of the mechanisms by which drugs of abuse produce addiction. This information can, in turn, be used to better understand addictive disorders in people and to develop more effective treatments.

Steven E. Hyman - Regulation of Gene Expression by Psychostimulants and Dopamine: Transcription Factor CREB is a Key Molecular Switch. Addiction likely results from adaptations that occur in multiple brain circuits in response to excessive bombardment by drugs of abuse. Adaptations within the mesolimbic brain reward circuitry have been hypothesized to produce both sensitization and tolerance as well as motivational aspects of withdrawal. Based on the latency of onset and the long-lasting nature of these adaptations, it has been hypothesized that they involve regulated gene expression. One adaptation that may contribute to motivational aspects of withdrawal in response to psychostimulants is induction of the prodynorphin gene and dynorphin peptides in the striatum which might act via recurrent collaterals to diminish dopamine release. Prodynorphin gene expression has been shown to be increased in both rodent models and humans in response to psychostimulant administration.

We have taken a "nucleus-out" strategy to investigate the effects of cocaine and amphetamine on the brain. We have investigated the molecular mechanisms underlying prodynorphin gene expression in response to amphetamine and dopamine in the striatum because of the potential behavioral significance of this adaptation. The proclynorphin gene contains three upstream cyclic AMP response elements (CREs) and a putative noncanonical AP-1 binding site. These candidate regulatory proteins include the CRE binding protein, CREB, which can activate transcription after being phosphotylated on its critical serine 133, and proteins which bind AP-1 sites, including c-fos. It was known that cocaine and amphetamine activate c-fos gene expression in striatum. We found using double-label *in situ* hybridization that it was induced in the substance P/clynorphin expressing neurons within the striatum. Using an antiserum that recognized CREB only when it is phosphorylated on Ser 133, we found that both cocaine and amphetamine induce CREB phosphorylation in the dorsal striatum and nucleus accumbens in a D1 dopamine receptor-dependent manner. To investigate the mechanisms that could link either CREB phosphorylation to induction of the prodynorphin gene, we have utilized E19 embryonic rat primary striatal cultures. By transfection of prodynorphin constructs into our primary cultures, we found that three upstream prodynorphin CREs are required for regulation of the prodynorphin gene by dopamine in striatal neurons. By electrophoetic mobility shift assays we demonstrated that CREB protein binds to these CREs in striatal cell extracts, and is phosphorylated on SER 133 after dopamine stimulation in a D1 dopamine receptor dependent manner. The noncanonical AP-1 site that has been described within the prodynorphin promoter does not show significant protein binding basally or following stimulation by dopamine.

In dissociated cultures, dopamine produces a transient phosphorylation of CREB. Surprisingly, we find that *in vivo* five days of twice daily amphetamine administration (10 mg/kg) induces upregulation of CREB phosphorylation over the basal stale. In contrast, the same treatment suppresses c-fos mRNA below basal levels. Taken together, these data suggest that CREB phosphorylation is the major nuclear event coupling D1 receptor stimulation to induction of the prodynorphin gene. Because many genes contain CREs, the upregulation of CREB phosphorylation could be responsible for diverse adaptations within the dorsal and ventral striatum following chronic amphetamine administration.

The discussion following these presentations focused on how new neuro-imaging techniques using PET and SPECT can examine specific receptors in defined neuro-anatomical areas of the living human brain and on the possibilities for new treatment approaches based on delivering medications to specific brain regions or on targeting the intracellular second messenger systems and ultimately the genome itself.

INHALANT ABUSE: OUR LEAST UNDERSTOOD DRUG PROBLEM.

R. L Balster, P. A. Mary, C. G. Schütz, E. J. Moody and J. R. Glowa

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Inhalants are a subset of abused organic solvents which include volatile aliphatic, aromatic, and halogenated hydrocarbons, alcohols, phenols, glycols, ethers, ketones, and nitrites, as well as some gases. The ability of these agents to readily penetrate the central nervous system can result in behavioral effects that are rapid in onset, clearly detectable, and of considerable concern as to their abuse potential. Exposure to high levels can impair judgement and performance, endangering the abuser as well as society. Inhalant abuse can result in a diverse range of health problems, including behavioral changes ranging from sleep disturbances to the precipitation of psychotic-like symptoms. However, it is the marked increase in deaths associated with inhalant abuse that emphasizes the urgent need to better understand the effects of these agents. Inhalants are the only major class of drugs of abuse that are not regulated in the United States. Inhalant abuse is increasing and because of its unrestricted availability may serve as a 'gateway drug' for the abuse of other drugs. Although methods are becoming available to determine the abuse pottential of inhalants, very little is currently known of the behavioral or neuropharmacological effects associated with inhalant abuse. In addition, we are only now gaining insight on the epidemiology of inhalant abuse. This symposium was designed to provide a broad introduction to inhalant abuse, emphasizing recent research issues. Different speakers addressed each of these issues, emphasizing that a wide range of expertise has begun to focus on our least understood drug abuse problem.

Dr. Philip May spoke on the epidemiology of inhalant abuse in the Southwestern United States, an area well-known for having relatively high numbers of inhalant abusers. He introduced the audience to the large number of inhalants that are abused, including toluene, nitrous oxide, ether, and gasoline. In addition, Dr. May developed an epidemiological cross-section of the typical inhalant abuser in the Southwestern United States, and well as the pattern of drug abuse in these individuals. These observations provided an extremely interesting linking hypothesis to the more basic areas of research to follow. For example, his research has noted that inhalant abuse is often associated with polydrug abuse. As inhalants are often relatively easy to obtain, their abuse may either set the occasion for, or be a consequence of, other forms of drug abuse. For example, alcohol is typically IN available during Sundays, holidays and early in the day. In addition, it may only be sold in certain locations, further restricting availability. At times and places when alcohol is not available, the incidence of inhalant abuse is greatly increased. Dr. May suggested that inhalant abuse may substitute for alcohol, or even other forms of "hard" drug abuse, when those drugs are not available. This term, substitution, became increasingly prevalent in subsequent presentations.

The second speaker, Dr. Christian Schütz, presented an experimental approach to analyzing epidemiological data from large databases such as DAWN and the National Household Survey on Drug Abuse. These surveys, which utilize very large sample sizes, are quite stable from year to year, allowing predictions to be made. For example, Dr. Schütz recently reported that inhalants abuse may serve as a vulnerability marker for intravenous drug abuse. A history of inhalant abuse increases, by more than five times, the likelihood that the same individual abuses drugs intravenously. When combined with marijuana use, this factor increases such that an individual with a history of both marijuana and inhalant abuse is 88.6 times more likely to have injected drugs. There has been considerable concern that the widespread availability and relatively low cost of inhalants may predispose individuals toward the development of a substance-dependent lifestyle, promoting the use of "harder" drugs.

Further studies were directed at comparisons of U. S. trends in inhalant abuse and world trends. Inhalant abuse is on the rise, and the increase in rate of drug abuse is greater in non-minority populations. Males are much more likely to abuse inhalants than females, especially younger (~ 13 years old) males.

Dr. Robert L. Balster presented an overview of the behavioral effects of inhalants. His early work focused the stimulus effects of inhalants, and he described how parenteral or inhalation exposures to inhalants can serve as discriminative stimuli. Since the discriminative effects of drugs may be related to their abuse potential, this provides one approach to assess the abuse potential of inhalants. Dr. Balster described how the stimulus effects of toluene, ethanol, trichloroethane, and halothane, but not isoamyl nitrite and fluroethyl, generalize from (or substitute for) those of classical sedative/hypnotic drugs, such as pentobarbital and ethanol. Another method of assessing the abuse potential of these drugs may be their ability to either stimulate or depress different behaviors. Dr. Balster described how the effects of several inhalants differ in their abilities to increase and decrease locomotor and schedule-controlled behaviors of mice.

Dr. Balster also reviewed direct experimental demonstrations of the reinforcing effects of a number of inhalants, including toluene, nitrous oxide, ether, chloroform, lacquer thinner and ethyl alcohol. Although these studies emphasize that inhalants can serve in much the same manner as conventional reinforcers, few other reports of this type exist due to the difficulty of arranging accurate inhalation exposures. Thus, those types of studies in which indirect measures of abuse potential can be obtained are likely to be very practical in terms of screening inhalants for abuse porential.

The last speaker was Dr. Eric Moody, who spoke of the neurochemical consequences of inhalant exposure, drawing upon his considerable work on the neuropharmacological effects of volatile anesthetics. His presentation discussed potential neural mechanisms of inhalant effects. Initially this analysis focused on GABAergic effects of inhalants. Both this group at NIH, as well as the group at MCV (Dr. Balster), had previously demonstrated that inhalants share effects with benzodiazepines, barbiturates, and alcohol. This suggested that some inhalant effects may directly involve the $GABA_A$ receptor. Inhalants also share behavioral effects with volatile general anesthetics, including abuse potential. While there is little agreement on how general anesthetics act, the Meyer-Overton theory relating fat-partitioning and potency of these agents relied on membrane disordering effects had been the generally accepted hypothesis until most recently.

Dr. Moody presented some more recent work suggesting that anesthetics exhibit a stereoselective effect, potentially challenging this notion. For example, the demonstration that (+) and (-) isoflurane exhibit significant differences in their anesthetic potencies provides compelling evidence for the hypothesis that proteins, rather than lipids, are the primary site of anesthetic action. The ability to separate activity with optical isomers provides potentially important new tools to discriminate among potential molecular targets of anesthetic action.

Dr. John R. Glowa provided a summation of the proceedings. A single theme that ran throughout these presentations was the ability of inhalants to substitute for other classical sedative/hypnotic drugs of abuse. This observation was seen with humans substituting inhalants for other drugs of abuse, when the latter were not available. Substitution was also clearly seen in the drug discrimination studies of Dr. Balster. The ability of behavioral studies to document this effect is important, and furthermore, their ability to link the effect with neurochemistry allows for a greater understanding of mechanisms. While inhalants clearly exhibit reinforcing effects, little is known of how these effects are directly associated with their abuse potential. As such, it is imperative that we continue to devise methods similar to those described by Dr. Balster to screen candidate inhalants for abuse potential. Understanding neurobiological mechanisms may allow us to develop effective treatments for overdose and possibly add to our understanding of the underlying biochemistry of drug abuse in general.

In addition, Dr. Moody has identified several promising approaches to improving therapeutic effects of inhalant anesthetics. Identifying susceptible populations may also aid in the development of greater understanding of risk factors for abuse potential, as it is clear that drugs of abuse alone are not the problem. Hopefully, this symposium will have set the stage for further discussions and cross-disciplinary collaborative efforts that will widen our knowledge of the many factors that contribute to inhalant abuse.

SUMMARY

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THE DOCUMENTED ROLE OF PHARMACOGENETICS IN THE IDENTIFICATION AND ADMINISTRATION OF NEW MEDICATIONS FOR TREATING DRUG ABUSE

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The identification and use of new medications to treat drug abuse holds great promise in that the recognition sites for all of the drugs of abuse have been identified and cloned. One of the major advances within the last five years has been the characterization of a multiplicity of liver and brain enzymes that can affect the metabolism of medications and drugs of abuse via both CYP450 induction and inhibition. This symposium brings together for the first time leaders from molecular biology, pharmacogenetics, *in vitro* and *in vivo* metabolism, pharmacology, medications development, and clinical treatment to provide an integrated perspective to accelerate the identification of new medications to treat drug abuse

Inter-Individual Difference In Drug Metabolism: A Factor In Variable Response to Drugs And Medications (R. L. W.) A full understanding of the role of cytochrome P450 (CYP450)-based drug metabolism in the clearance of drugs of abuse may be critical to understanding differences between individuals in their vulnerability to addiction and the development of therapeutic strategies. At the present time, drugs of abuse are among the least studied with respect to the role of CYP450. Recent advances in genetics, molecular biology and drug metabolism have made it possible to determine the factors leading to variability in response to many medications. The greatest advances have been made by determining the exact hepatic enzyme responsible for the metabolism of medications and the role of polymorphic distribution of the activity of these enzymes (termed CYP450) have been identified and divided into several major families. Several of these enzymes (CYP1A2, 2C19, 2D6, 2E1 and 3A4) have been characterized extensively in clinical and in *vitro* experiments. Knowledge of an individual's phenotypic expression for one or more of these enzymes can often explain 1) lack of response to therapy, 2) adverse reactions and 3) drug-drug interactions (in some cases lethal).

Identification of Substrates, Inhibitors and Determination of Clinical Importance (E. M. S.) At least 30 medications, many of them derived from plant alkaloids, have been shown to be oxidized by CYP2D6, including tricyclic antidepressants, some neuroleptics, beta-blockers and anti-arrhythmic agents such as perhexiline, flecainide and encainide. Several drugs of abuse, codeine, hydrocodone, oxycodone. dextromethorphan, and p-methoxyamphetamine, are known to be metabolized by this same enzyme. CYP2D6-mediated metabolism of these medications and drugs of abuse are known lo be a major source of pharmacokinetic variations and hence variation in pharmacological effect. A number of drugs of abuse are known substrates (*e.g.,* codeine, hydrocodone, p-methoxyamphetamine, amphetamine) or inhibitors (*e.g.,* cocaine, pentazocine) of CYP2D6. For some of these drugs, the pharmacokinetic dilferences due to CYP450 polymorphism will be so profound that they are likely to exceed pharmacodymamic sources of variation in response. For other drugs (*e.g.,* the metabolism of hydrocodone to hydromorphone, codeine to morphine, oxycodone to oxymorphone), CYP2D6 may not only contribute importantly to the overall clearance of the drug, but may catalyze the formation of highly active metabolites. The consequences of absent or inhibited CYP2D6 for any particular drug will depend on the relative activity of the parent drug and its various metabolites. In some cases, the pharmacology of the metabolite is qualitatively similar to the parent drug (*e.g.,* hydrocodone to hydromorphone, codeine to morphine); in other cases, the pharmacology is different (*e.g.,* dextromethorphan to dextrorphan); more usually, it is not properly understood (*e.g.,* p-methoxyamphetamine to 4-hydroxyamphetamine). In addition, CYP2D6 occurs within the CNS. Its role in the brain is unknown, but potential formation of active drug metabolites at their site of action makes the presence of CYP2D6 here of great functional significance and could account, in part, for large inter-subject

variability in the pharmacodynamic effects of psychoactive drugs leading to both risk factors and protection factors in drug abuse and toxicity from drugs of abuse.

It is hypothesized that:

- •The genetically determined activity of CYP2D6 which results in the "extensive metabolizers" (EMs 90%) and "poor metabolizers" (PMs 10%) of some drugs of abuse is both an important risk-factor and protection-factor in drug abuse and toxicity from drugs of abuse.
- •Certain inhibitors of CYP2D6, or the PM state itself, will result in unexpected toxicity from drugs of abuse (*e.g.,* p- methoxyamphetamine [PMA]) or may have utility in the treatment of drug dependence (*e.g.,* preventing activation of a pro-drug, such as codeine, oxycodone).
- •CYP2D6 may play an important neuroregulatory role in the brain, and may modulate brain functions important in drug reinforced behavior or neurotoxicity.

Clinical Example: Interactions of Concomitant Medications on Methadone Concentrations (J. T. P.) For many years methadone maintained patients have been destabilized by concomitant medications capable of the induction of CYP450 enzyme activity in the liver. Often clinicians were reluctant to effect appropriate interventions, including the use adequate doses of methadone with the necessary frequency needed to maintain stability. Patients are fared with the choice of opioid withdrawal syndrome, risk of seizures (non-compliance in use of essentials medications), or self medication with heroin or street methadone. Such patients have even been administratively withdrawn and discharged from methadone maintenance pharmacotherapy, often as "treatment failures". The increased availability of affordable and reliable quantitative methadone determinations has made objective clinical management possible. A basic understanding of methadone pharmacokinetics, drug-drug interactions and clinical relationships of efficacy lo levels of methadone are requisites to effective treatment. Early studies by Kreek and others established a peak-to- trough ratio of 2 or less (T-1/2≥ 24 hours) per dosing interval (usually 24 hours) in optimally maintained patients. There is growing consensus that while trough levels of 150 to 200 ng/ml will prevent withdrawal and provide stability for many patients, levels of 400 ng/ml may be needed to achieve effective levels of cross tolerance or "blockade." Of greatest clinical significance is the rate of change over the dosing interval (peak to trough ratio or half-life). Clinical interventions can best be illustrated with brief case histories. Patient A was admitted using $150 heroin daily. He was disabled and under treatment with carbamazepine for a severe seizure disorder. Based on clinical presentation, the daily dose of methadone was gradually adjusted to 180 mg daily. At that time he was symptomatic in less than 24 hours. Initial methadone levels were 118 ng/ml at 3 hours and <25 ng/ml at 24 hours. It was clear that a single 24 hour dose of any size would not suffice. Eventually the patient was clinically stabilized at methadone 100 mg and cimetidine (a CYP2D6 inhibitor) 300 mg every 6 hours. Cimetidine was effective in the reducing the rate of methadone metabolism. Levels at 2-3 and 6 hours were 147 and 116 ng/ml with a ratio of 1.26. Low but relatively "flat" levels over the dosing interval. Patient B, a 39 year old female, was admitted as an insulin dependent diabetic with a severe seizure disorder, alcoholism in remission, chronic opioid addiction, bulimia, anxiety, and depression. Phenytoin 400 mg daily provided adequate control of seizure activity. After 12 days her 3/24 hour methadone levels were 38/0 ng/ml at a dose of 100 mg daily. With an increase to 100 mg q 12 h the 3/12 hour levels were 38/0 ng/ml. The addition of cimetidine contributed to a phenytoin intoxication and was abandoned in favor of stabilization with methadone alone. Methadone was gradually increased to 100 mg q 6 h resulting in dramatic clinical improvement as well as 3/6 hour levels of 224/101 ng/ml 2.22, suggesting a T-1/2 of about 6 hours. The patient is now doing well at 120 mg of methadone every 6 hours.

Clinical Example: The Cyp450 Pathways of LAAM (D.E M.) The metabolism of –α– acetylmethadol (LAAM) to its N-demethylated product, norLAAM, appears necessary to provide the extended pharmacodynamic half-life that distinguishes LAAM from methadone, providing for alternate day dosing. The identification of the CYP450 isozyme(s) involved in LAAM metabolism is important to define the efficacy and safety issues of LAAM therapy. The production of norLAAM (after incubation with LAAM) and dinorLAAM (after incubation with LAAM or norLAAM) can be detected in human liver microsomes (HLMs) supplemented with NADPH, an essential cofactor for CYP450-mediated reactions. In HLMs from four different sources, product formation varied - 20-fold suggesting large individual differences in the rate of LAAM and norLAAM metabolism. Coincubation of HLMs with LAAM or norLAAM and CYP450-selective inhibitors revealed that

ketoconazole, an inhibitor of CYP3A, is a potent inhibitor (> 80% inhibition) of both N-demethylations. Ketoconazole inhibition was concentration dependent with an IC_{50} of 1 μM. Diethyldithiocarbamate at 100 μM., a CYPZE1 inhibitor, and sulphaphenazole at 100 μM., a CYP2C9 inhibitor, also had modest inhibitory effects (30% inhibition) on LAAM N-demethylation to norLAAM. Only ketoconazole affected norLAAM N- demethylation. Comparing cDNA-expressed CYP 1A2, 2C9, 2D6, 2E1 and 3A4 revealed that CYP3A4 had the greatest activity for N-demethylation of LAAM and norLAAM. The cDNA-expressed CYMD6 had some activity for N-demethylation of LAAM and norLAAM, and the 2E1 some activity for LAAM. These results suggest that CYP3A4 is the major contributor to LAAM and norLAAM N-demethylation. This CYP450 is well known for its inducibility and as a site for drug-drug interactions, and appropriate precautions are needed to preclude potential adverse effects in patients receiving LAAM and comedications known to influence CYP3A4 metabolism. A similar approach is now being employed lo define CYP450 involvement in the N-demethylation of methadone.

Clinical Example: *In Vitro* Determination Of Cyp450 Metabolic Pathways (J.C.) Drug-drug interactions are an important consideration for safety and efficacy of therapy. Patients routinely take multiple concomitant medicines, either continuously or episodically. One of the most common types of interactions is interference of one drug with another medications metabolism. For new medication development, we are interested in two types of questions: (1) Does administration of the new medication inhibit known pathways for other, commonly-used medications? and (2) What are the pathways for metabolism of this new medication? Because of the large number of potential combinations, it's not practical to clinically screen for all drug-drug interactions. Fortunately, in both cases, most of the necessary information can routinely be obtained with experiments *in vitro,* rather than clinical studies. While the growing number of reports of studies of drug-drug interactions (positive or negative) are very helpful for specific therapeutic situations, the sheer volume presents a large challenge for prescriber awareness. One solution is a conceptual framework which will provide generalizations across a class of medications and permit some inferences regarding expected effects (or lack of effects) even for medications which have not been directly studied for interactions. Although the major focus in medication development is avoidance of safety problems from drug-drug interactions arising from largely unintentional co-administration of drugs, there are also circumstances in which the metabolism of a drug might be intentionally inhibited. For example, the requirements for patient visits to the clinic for a medication such as LAAM are at least partially driven by the half-life of LAAM in the body. If the metabolic inactivation can be slowed (e.g., by concomitant use of ketoconazole), then thrice-weekly clinic visits might be replaced by twice-weekly or weekly visits, assuming that all other patient-specific conditions are acceptable.

Brain Cyp450s: Potential Role In Drug Abuse And Its Treatment (R.F.T.) Medication metabolism has been studied extensively in the liver, where variability leads to inter-individual differences in plasma medication levels, medicate response and toxicity. Recently medication metabolism in extrahepatic tissues, such as the brain, has been receiving increasing attention. It is generally assumed that metabolism in the brain does not play a major quantitative role in the overall metabolism and clearance of xenobiotics. Brain metabolism may, however, have a dramatic impact on drug and metabolite concentration in close proximity to central nervous system (CNS) receptors and therefore importantly affect drug actions and toxicity. CYP450s in the brain are exquisitely sensitive to medications and drugs of abuse and respond with complex and specific patterns of induction and expression. CYP4S0s have been identified in the human, rat, dog, rabbit, mouse and monkey brain using spectrophotometric, catalytic, molecular and immunologic techniques. Brain tissues include members from all of the liver drug-metabolizing CYP450 subfanilies. The total brain CYP450 content is low, with estimates around 1-3% of the liver; specific isoforms CM reach levels up to 10% of their hepatic counterparts in some brain regions. The composition and ratios of enzymes in the CNS differ from those in liver resulting in distinct metabolic profiles in the two tissues. Then is considerable evidence for unique neuroanatomical distributions for each specific brain CYP450 isozyme and resultant enzyme activity. Individual CYP450 can be found in glial and/or neuronal cells, and are frequently clustered within specific cell types in a region-specific manner. They are also found in microvessels and may play a role in the blood-brain barrier. Differences in regulation of CNS CYP450 occur between different brain regions, cell types, cell membranes, species and sexes. Brain and liver regulation of CYP450s differs dramatically, with hepatic inducers (*e.g.,* phenobarbital or methylcholanthrene) increasing, decreasing, or not altering the levels of brain

CYP450s, in a region-, isozyme-, and cell-specific manner. Brain CYP450s can also be induced by agents which do not induce the same or any liver CYP450s, and non-inducible liver CYP450 can be inducible in the brain. Endocrine regulation of some CNS CYP450s has also been observed. There are marked differences between species and genders for some CNS CYP450s and not for others. The distinctive CYP450 localization and regulation may have profound consequences for clinical therapy, drug development and toxicology. Interindividual variation in hepatic CYP450s has already been demonstrated to play a role in the variation of drug response and toxicity. Organ-, region-and cell-specific localization and regulation of brain P450S may have a major impact on the toxicity of therapeutic and non-therapeutic agents, solvents and environmental pollutants. It may also explain the Interindividual variation observed in the response to psychoactive drugs and in the susceptibility to drug dependence. Our present and future studies are aimed ill improving our understanding of the activity, biochemistry, molecular regulation and importance of brain CYP450s, ultimately leading to the development of methods for predicting and preventing the individual response, toxicity and abuse of psychoactive drugs.

Impact for Future Research (C.V.G.) It is obvious from the dates presented in this symposium that pharmacogenetics and the CYP450 systems in the liver and brain can play a major role in many aspects of medication discovery, development and use. Pharmacogenetics may even play a major role in explaining the vulnerability of certain individuals to becoming addicted to drugs. Several of the key areas impact on the search for new medications, beginning with animal screens. Key R & D decisions include "Which animal species and which strain would be most predictive of the human situations'?" The metabolic profile in humans has impact for the medicinal chemist as new compounds are designed to either take advantage of, or avoid, the natural metabolic fate of naturally occurring and synthetic pharmaceutical agents. One of the most important decisions in new medication development is the selection of safety assessment candidates (SACs). In this decision the pharmacogenetics of the intended patient population must be taken into account lo ensure the highest probability of technical success as the SAC gains forward motion toward the clinic. More and more the question, "What are the other medications that this population routinely (or occasionally) take, and what do we know about the interactions of our new medication and those medications?" is being asked before the final decision is made to expend the $M1-2 necessary to prepare and file an IND. The design of the first clinical trials now include earlier assessments of the human metabolic profile of the clinical candidate. This early knowledge can accelerate the ability to identify the appropriate dose and dose regimen-the ultimate goal of Phase 2 trials. Perhaps the most exciting frontier is the use of concomitant medications to adjust the metabolic profile, and hence the serum, tissue and CNS levels of the medication being prescribed.

Pharmacogenetics, a field that began as a curiosity as to why some individuals reacted differently to certain medications, has now come full circle with the ability of being able to not only predict how a patient will handle a particular medication, but to be able to manipulate the metabolic fate of one medication by the addition of a second. The ultimate product of the original Curiosity may lead to the understanding of both drug abuse risk and protective factors.

SYMPOSIUM: OPIOID RECEPTOR SIGNAL TRANSDUCTION IN NARCOTIC TOLERANCE AND DEPENDENCE.

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Narcotic drugs are highly effective analgesics, but their addictive properties lead lo widespread illicit use. By interacting with the μ opioid receptor, narcotics induce a signal transduction cascade which results in acute effects, including analgesia. Simultaneously, and more gradually, a tolerant-dependent state is induced along with drug seeking behavior as the main elements of narcotic addiction. Whether the acute and chronic narcotic effects are based on distinct mechanisms and can be separated is under intense study. Recent advances in understanding opioid receptor sigmal transduction and the cloning of the opioid receptor genes have provided new insights into the mechanisms contributing to narcotic tolerance and dependence. This symposium focused on the structure and function of the μ opioid receptor, its signal transduction, downstream signalling cascades, the regulation of receptor activity in tolerance and dependence, and bimodal effects on the cAMP second messenger system. Taken together, these results provide an integrated understanding of narcotic tolerance and dependence that could lead to improved management of narcotic addiction.

μ Opioid Receptor: From Molecular Cloning to Cellular Signaling. *Lei Yu*, Department of Medical and Molecular Genetics, Indiana University School of Medicine

The μ opioid receptor is the major cellular target of opioids with high abuse liability, such as morphine and fentanyl. Cloning the μ receptor gene has afforded the opportunity to study its signal transduction and regulation at the molecular level (Chen *et al.,* 1993). To explore the molecular mechanisms underlying μ receptor-mediated tolerance and dependence at the cellular level, genes encoding the μ receptor and a G protein-activated inward rectifier K^+ channel were co-expressed in *Xenopus* oocytes from the corresponding cDNA clones. Application of opioid ligands elicited K^+ currents as measured by the voltage clamp technique, indicating that in this reconstituted system, the μ receptor is capable of opening the inward rectifier K^+ channel. The μ receptor-mediated K^+ current undergoes desensitization, as the K^+ current from the second opioid stimulation is only 70-75s of the first current. Activation of protein kinase A between the two opioid stimulations blocked the onset of desensitization, whereas activation of either protein kinase C or Ca,calmodulin-dependent protein kinase enhanced desensitization. These results indicate that when expressed in *Xenopus* oocytes, the μ receptor-K+ channel coupling can be modulated by various protein kinases, and such mechanisms may contribute lo narcotic tolerance in dependence in neurons.

Regulation of the cAMP Signaling Cascade in Narcotic Addiction *Katherine L. Widnell* and Eric J. Nestler, Laboratory of Molecular Psychiatry, Departments of Psychiatry and Pharmacology, Yale University School of Medicine

Chronic administration of morphine alters certain G proteins and components of the cAMP intracellular messenger system in the brain. For example, alterations in these proteins occur in the nucleus accumbens (NAc), a brain region implicated in the acute reinforcing properties of opiates and possibly also in the long-term changes associated with opiate addiction (Self and Nestler, 1995). Recent work has provided direct evidence for a role of opiate regulation of Gi α and the cAMP pathway in drug reinforcement and addiction: intra-NAc administration of agents that inhibit Giα or activate cAMP-dependent protein kinase increase heroin self-administration, whereas agents that produce the opposite effect decrease drug self-administration. We are currently investigating the molecular mechanisms involved in chronic adaptation lo morphine by focusing on regulation of the transcription factor CREB (cAMP response element binding protein) in the NAc. The transcription factor CREB mediates many of the effects of the cAMP signaling pathway on gene expression by cooperatively binding to CRE (cAMP response element) sites found in the promoter regions of many neurally expressed genes. Based on evidence in a neurally-derived cell line that CREB expression is

regulated by the cAMP pathway (Widnell *et al.* 1994), we examined CREB regulation by morphine in the NAc. Chronic morphine administration was found to decrease levels of CREB immunoreactivity in the NAc, but not in other brain regions studied. The functional significance of the observed morphine-induced CREB down-regulation was examined by use of an antisense oligonucleotide strategy. Antisense-induced reductions in CREB levels mimicked the effect of morphine on Giα, but not on CAMP-dependent protein kinase catalytic subunit. All other signal transduction pathway proteins tested were unaffected by this treatment. Our results suggest a role for CREB in mediating some of the effects of morphine on the cAMP pathway in the NAc.

μ Receptor Regulation by Phosphorylation Underlying Narcotic Tolerance and Dependence. *Wolfgang Sadée*, School of Pharmacy, University of California San Francisco, CA.

Whereas receptor phosphorylation is generally assumed to induce desensitization, we have proposed the hypothesis that μ opioid receptor phosphorylation results in sensitization or constitutive activation, i.e., signaling activity in the absence of any agonist (Wang *et al.,* 1994). The acute response to narcotic agonist stimulation, such as analgesia, depends on signal transduction via G proteins, while the concurrent, gradual conversion of the μ receptor to a phosphorylated, activated state, termed μ*, is proposed to underly the development of narcotic tolerance and dependence. A polyphosphorylated, activated receptor species, μ*, could be unexpectedly stable over prolonged time period if it functions as an activating substrate of G protein receptor kinases (GRKs) (Sadée *et al.,* 1994). Direct measurements of μ receptor phosphorylation revealed a high bnsal rate of phosphorylation (Arden *et al.,* 1995) suggesting the presence of an activated state, μ*. Basal phosphorylation was further enhanced by morphine pretreatment of epitope tagged μ opioid receptors transfected into HEK 293 cells (Wang *et al.,* unpublished). The kinase inhibitor H7 blocked μ receptor phosphorylation, and it also reversed acute morphine tolerance and dependence in mice without affecting morphine analgesia. In contrast, the congener H8 was without effect on basal μ* activity in vitro and failed to block acute morphine tolerance and dependence *in vivo* (Wang et al. 1994). Since both H7 and H8 inhibit PKA and PKC, these protein kinases may not play a role in μ* formation. Agonist stimulated conversion of the μ opioid receptor to a rather stable, phosphorylated, and sensitized-activated state, μ*, represents a new paradigm of receptor regulation with a possible role in narcotic addiction. Distinct mechanisms underlying acute and chronic narcotic effects offer the promise of developing safe analgesics and effective therapy of narcotic addiction.

Bimodality of Opioid Agonist Effects: Role of Phosphorylation in Acute and Chronic Action. *Alan Gintzler*, Department of Biochemistry, State University of New York Health Sciences Center, Brooklyn, NY

Opioids have a dual action on both the electrically stimulated release of methionine-enkephalin from and formation of cAMP in myenteric neurons. Either an enhancement or an inhibition of enkephalin release (Gintzler and Xu, 1991) or cAMP formation (Wang and Gintzler, 1994) can be observed depending on the concentration of opioid agonist that is used. Low doses (nanomolar) enhance evoked transmitter release and cAMP second messenger formation whereas higher concentrations (μM) inhibit these neuronal responses. Opioid stimulatory and inhibitory actions can be attenuated by naloxone (0.1-1.0 μM) indicating that both are mediated by opiate receptors. The finding that opiate receptors are positively as well as negatively coupled to adenylyl cyclase is novel because hitherto the ability of opiates to depress adenylyl cylase activity (and neurotransmitter release) has been considered to be the predominant mode by which these compounds act.

Chronic *in vivo* exposure to morphine results not only in the loss of inhibitory opioid responsiveness but in the reversal of inhibition to enhancement, i.e., opioid excitatory responses are predominant (Wang and Gintzler, 1995). The stale of phosphorylation is a critical determinant of the balance between positive and negative opioid modulation of stimulated cAMP formation. In opiate naive tissue, treatments that enhance phosphorylation not only attenuate sufentanil inhibition of evoked cAMP formation but reverse it to a facilitation (as occurs following chronic *in vivo* morphine exposure). Conversely, treatments of 'addicted' preparations with inhibitors of protein kinase C, but not protein kinase A (that would be expected to reduce

the level of phosphorylation) abolishes the previously observed reversal of opioid inhibition to enhancement and restores sufentanil inhibitory responsiveness. These results underscore the relevance of opioid bimodality to the manifestation of tolerance/dependence and suggest that augmented phosphorylation via protein kinase C is a critical determinant of some of the sequelae of chronic morphine exposure.

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THE CONFLICTS FOR PARENTING DRUG DEPENDENT WOMEN - WHAT DOES RESEARCH SHOW US?

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Being a parent and a drug dependent woman presents many conflicts. Research studies under the auspices of the National Institute on Drug Abuse and others have defined the characteristics of parenting behavior among cocaine-using women. Current research is defining, through assessment of maternal lifestyles, the potential for adequate parenting by drug dependent women. Historical accounts provide information concerning the lack of gender-specific treatment modalities and the effect of punitive approaches taken against drug abusing women. In the last few years many legal issues have confronted parenting drug dependent women. Although women in the past have been unable to obtain the treatment necessary to enhance their parenting skills, with the practical information available and present and future research, it will be possible to enhance parenting within the context of drug abuse treatment. This symposium summarized the historical facts, the myths and the research available with regard to parenting within the context of drug dependence in women.

The years between 1914, when the Harrison Narcotic Act was passed, and 1919, when the Supreme Court ruled in *Doremus and Webb,* are a defining period in American drug history. Prior to those years, when drugs were essentially legal and available, women constituted approximately two-thirds of America's opiate addicts and a significant fraction of users of chloroform, *chloral* hydrate, cocaine and cannabis. After 1919, when drugs were *de facto* criminalized, women' treatment options were limited to private sanitaria, individual physicians or pharmacists who were willing to risk prosecution, or one of 44 drug maintenance clinics which existed between 1919 and 1923. When those clinics closed, formalized treatment for women during the Classic Era could be found only at the Lexington Federal Farm. The 1960s saw the development of treatment modalities, including civil commitment, detoxification, therapeutic communities, spiritual programs, outpatient and inpatient programs, correctional treatment programs, and most importantly, methadone maintenance programs. In the 1970s gender-specific programs for drug-dependent women were developed, but societal catastrophies of the 1980s and 1990s, such as family fragmentation, "crack," AIDS, the resurgence of heroin, and a decrease in funding for education, prevention and treatment of drug dependence drove women further into the underworld and increasing involvement with the criminal justice system. The small fraction of Federal drug-lighting dollars devoted to treatment of drug-using women speaks to the continuing need to highlight this issue.

The literature on the effects of prenatal drug exposure and child outcome is inconclusive because of a paucity of methodologically sound studies and because models have failed to consider the role of parenting and the larger caregiving environment. One of the basic premises of child rearing and intervention models is that infant behavior is part of a communication system with the caregiving environment. This is a dyadic and dynamic system in which feedback from one partner to the other is used lo regulate this system and in most cases, to insure normal developmental outcome.

In early work with drug exposed infants, this complexity was not 'appreciated and main effect or linear models were used. It was thought that drug exposure per se led to poor developmental outcome and if the mother was considered at all, it was thought that she could only lower the developmental outcome of the child. 'the Maternal Lifestyles Study, a multicenter, prospective longitudinal study funded by NICHD, NIDA, ACYF and CSAT is attempting to address these issues by studying the effects of prenatal drug exposure to cocaine and/or opiates and are following a group of exposed infants (subdivided into birthweight categories) and a comparison group at developmentally appropriate ages for at least the first three years of life. With the results of such methodologically sound studies with adequate numbers of subjects, the chance of defining more precisely the outcomes of infants exposed to drug dependence *in utero* has markedly increased.

How cocaine use affects mothers' ability to attend and respond to their infants during mutual interactions has not been extensively studied. On-going research at the Yale Clinical Study Center has addressed the evaluation of characteristics of parenting behavior among cocaine-using women. The face-to-face interactions of 42 currently cocaine-using mothers and their prenatally-exposed infants were compared to those of 39 non-cocaine-using mothers at three and six months of age. Coders blind to the mothers' drug use status scored three minutes of face-to-face interactions for 10 measures of maternal interactive behavior, three measures of maternal interruption of the interaction, and seven measures of infant alertness, vocalization, affective range, and responsiveness. Varimax rotation of the principal components of maternal interactive behavior resulted in two factors describing maternal attention to the infant and extension of the interaction. A single principal component of the infant measures described infants' readiness to interact.

Analyses were covaried for differences in maternal age, education, other drug use including alcohol, tobacco, and marijuana, and infant birthweight and perinatal complications. At three and six months, cocaine-using mothers were less attentive and less often extended interactions. They also more often interrupted interactions by looking away, redirecting the infant, or withdrawing; and their infants were less interactive. Between three and six months, cocaine-using mothers became less attentive during the interaction and more frequently intempted interactions, while non-cocaine-using mothers showed no change or improved in attending and in maintaining interactions. Similarly, by six months, the infants of cocaine-using mothers were more interactive. As a result of these studies, it is suggested that cocaine use represents a significant risk for diminished parental attention and responsiveness to the infant.

Although the need to address parenting within treatment programs has been recognized for the past 20 years, it is only recently that it has been widely implemented. The need to include parenting services has been based on, 1) the risk of developmental and behavioral problems for children born to substance- abusing mothers and, 2) an attempt to reduce barriers to women's participation in treatment related to the presence of dependent children.

Parenting services may take many different forms and combinations, such as dyadic prevention/intervention, developmental day care/child care, therapeutic child cue, parent support groups, parent-child activity, parent education, and parenting curriculums. Whatever form is used, parenting services should reflect a developmental model which assesses mothers' and infants' behavioral strengths and weaknesses and emphasizes sensitive, responsive parent-child interaction as an essential element to both the child's and parent's development.

In order to integrate parenting services within a treatment program it is recommended that they employ a family-centered treatment model. Central elements to this approach are honoring the racial, ethnic, cultural, and socio-economic diversity of families; building on the strengths unique to each family; and respecting different methods of coping. A family-centered approach enables parenting services for substance abusing women to recognize that each mother-child dyad embodies a unique configuration of both strengths and vulnerabilities; to be driven by collaborative strategies that consider personal, familial, and social factors; and to be provided within a multidisciplinary team that includes treatment clinicians and child development specialists in partnership. Until we can provide such services for drug dependent parenting women, current attitudes and legal practices should be tempered.

However, judges, legislators and prosecutors, like the public in general, have obtained most of their information about drug dependent pregnant and parenting women from the popular press. The coverage of the so-called "crack epidemic" and "crack baby" crisis has been, to a large extent, inaccurate and alarmist. Careful research and measured responses have not been widely covered and the prevailing assumption is that children exposed prenatally to "crack" are inevitably and irremediably damaged. The reaction to the problems of drug addicted pregnant women have thus been largely punitive. Hundreds of women have been prosecuted on unprecedented theories of fetal abuse and drug delivery through the umbilical cord. These prosecutions continue despite the fact that no appellate court in the country has upheld one.

Thousands of women have also been reported under civil child neglect laws and investigated for being neglectful or abusive parents based solely on a positive urine toxicology specimen at the birth of the child. African-

American women have been arrested and reported disproportionately to authorities despite evidence that white and black women use illegal substances at approximately the same rate. Judges often assume, incorrectly, that drug dependent pregnant women have access to appropriate drug treatment, to contraceptive and abortion services and prenatal care. Moreover, they do not view addiction as a disease or understand that relapse may be part of recovery. The public policy statements of leading medical and public health organizations opposing punitive responses has helped. Continued prosecution of pregnant women, cutbacks in services for pregnant and parenting drug users, and the continued belief among many leaders that children's physical and emotional health problems can be blamed exclusively on cocaine or other drugs suggests the need for extensive judicial and public education and organized opposition to punitive approaches to this health problem.

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NEUROTOXICITY AND NEUROPATHOLOGY ASSOCIATED WITH COCAINE/PSYCHOSTIMULANT ABUSE

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Dependence on psychostimulants (cocaine and amphetamines) is a chronic neuropsychiatric disorder, typically associated with other types of substance dependence and a variety of comorbid disorders, including anxiety, depression, anhedonia, attention deficit, antisocial behavior, and cognitive deficits, among others (rev. Majewska, 1995). Psychostimulant dependence, due to its clinical complexity, is extremely difficult to treat and is typified by a very high rate of relapse. So far, no effective pharmacotherapy for this disorder has been found, although some success in treatment has been reported with behavioral/psychotherapies. In order to develop an effective and comprehensive treatment strategy for psychostimulant dependence, we need to understand the magnitude and nature of neuropsychopathologies associated with this disorder. Hospital emergency reported complications of cocaine use include: seizures, optic neuropathy, cerebral infarctions, subarachnoid and intracerebral hemorrhages, multifocal and global cerebral ischemia, cerebral atrophy, and toxic encephalopathy/coma, among others (Daras *et al.,* 1991; Fredericks et al., 1991; Moody *et al.,* 1988; Pascual-Leone *et al.,* 1991). Systemic cocaine toxicity in lungs, liver and cardiovascular system (arrhythmias, myocardial necrosis and infarction, arteriosclerosis) also contribute to psychostimulant-induced neuropathologies.

Persistent, possibly permanent, deficits in blood perfusion and glucose metabolism, particularly in the frontal cortex, have been measured in chronic cocaine/stimulant abusers using neuro-imaging techniques, including PET, SPECT and MRI (Volkow, *et al.,* 1988; Bartzokis *et al.,* 1995; London *et al.,* 1995). The circulatory-metabolic deficits may ensue directly from cocaine-induced vasoconstriction of cerebral vessels as well as increased platelet aggregation and blood clotting (Kosten, 1995). Bartzokis and colleagues, employing MRI techniques, found evidence of multifocal strokes, ischemic attacks, and brain lesions, accompanied by an accumulation of iron and brain edema, particularly pronounced in basal ganglia and cerebral cortex, that were present in about 30 percent of treatment-seeking cocaine addicts (Bartzokis, *et al.,* 1995). Studies utilizing ^{31}P magnetic resonance spectrometry revealed that abstinent chronic cocaine abusers also show marked reduction of ATP/Pi ratio, particularly in the cerebral cortex, indicating bio-energetic deficits, similar to those observed in individuals who experienced cerebral hypoxia and ischemia (Chrisliansen *et al.,* 1994). These changes, which correlated with years and amounts of cocaine abuse, suggest that chronic psychostimulant abusers have dysfunctional mitochondria. This observation corresponds with evidence of increased urinary release of products of free radical lipid peroxidation in cocaine abusers (Knight *et al.,* 1988), which is a manifestation of impaired mitochondrial functions.

Mitochondrial dysfunction has been recognized as a critical factor contributing to development of various neuropathies and neurodegenerative diseases, including Parkinson's disease and other movement disorders, Alzheimer disease, organic dementias, and others. Persistent extrapyramidal movement disorders in chronic cocaine addicts, including dystonia, choreo-athletic movements (crack dancing), ticks and others, represent a convincing clinical evidence of psychostimulants' toxicity at basal ganglia (Bartzokis *et al.,* 1995). Bauer and collaborators described also a persistent hand tremor in abstinent, former chronic cocaine abusers, which resembled that observed in patients diagnosed with Parkinson's disease old correlated with the years and amounts of cocaine abuse (Bauer, 1995). This hand tremor, which may be an early manifestation of preclinical state of Parkinson's disease, corresponded with slower than normal reaction time, reduced amplitudes of p300 evoked potentials, persistent changes in eye movement (Bauer, 1995), and other encephalographic abnormalities in the population of abstinent former cocaine abusers (Herning *et al.,* 1995; Bauer, 1995). These multiple neuropsychiatric deficits, which appeared to be a consequence of long-term cocaine use rather than resulting from a premorbid condition, are convincing indicators of neurotoxic effects of cocaine and may be termed as "cocaine syndrome".

The clinical manifestations of neuronal deficiencies in cocaine addicts that persisted after prolonged periods of abstinence, correspond with the results of animal studies. In rats exposed continuously lo cocaine (three days, cocaine pellets), in a manner that mimics banging in addicts, striking axonal degeneration extending from lateral habenula along the fasciculus retroflexus toward the ventral tegmentum was observed and chronic amphetamine administration was associated with additional striatal lesions (Ellison *et al.,* 1995). In rats exposed chronically to cocaine, lasting depletion of brain monoamines, particularly dopamine (DA), reported (Hurd *et al.,* 1989; Beitner-Johnson and Nestler, 1991) rev. Majewska, 1995. The continual hypodopaminergic state, induced by cocaine, may result from a combination of several factors, such as prevention of DA reuptake by cocaine, compensatory down-regulation of DA synthesis, and possible degeneration of DA neurons. Also, in rats exposed chronically to cocaine persistent changes in cholinergic and GABA systems were noted (rev. Majewska, 1995), corresponding with behavioral abnormalities such as memory deficits, exaggerated fear and anxiety. Chronic cocaine abuse is also associated with changes in opioid system, including ever-expression of dynorphin and kappa-receptors, and under-expression of enkephalins (Hurd and Herhenham, 1993), which may contribute to incessant anhedonia/dysphoria reported in psychostimulant abusers.

Collectively, clinical and preclinical observations suggest that chronic use of cocaine/psychostimulants is associated with significant neuropathologies, which may be, in part, induced by chronic abuse of these drugs, and, in part, may be pre-existing. The premorbid states such as attention deficit hyperactivity disorder, post-traumatic stress disorder, or neuropathies resulting from lead poisoning or head traumas, all appear to contribute to individual vulnerability to stimulant dependence (rev. Majewska, 1995). Cocaine, per se, may induce neuronal deficiences by several neurochemical mechanisms, including: generation of neurotoxic free radical dopamine metabolites and free radical lipid species, mitochondrial impairments, and glutamate-mediated neurotoxicity, among others.

The appreciation of neuropathologies associated with cocaine/psychostimulant dependence may guide the strategies for development of effective treatments for this disorder. In this context, treatments that mimic actions of psychostimulants (a replacement therapy) are expected to aggravate or sustain cocaine dependence by potentiating the existing neurochemical imbalance. In contrast, treatments aiming to restore brain homeostasis and compensate for the existing neurochemical deficiencies, possibly with naturally occurring substances, supplements, or neurotransmitter precursors might be both safe and effective.

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CAFFEINE: A MODEL DRUG OF ABUSE

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The widespread use of culturally-sanctioned caffeine-containing foods presents an intriguing paradox. On one hand, it is the experience of most regular caffeine users that caffeine produces only rather subtle effects that are generally so well-woven into the fabric of daily experience that they are not clearly differentiated from the changes in mod and behavior associated with normal experience. On the other hand, caffeine is arguably the most robust form of drug self-administration known to man. Consider the facts: 1. Historically, use of caffeine-containing foods has been long-term, possibly dating back 5,000 years. 2. Also historically, use of caffeine-containing foods spread worldwide despite recurring efforts, motivated on moral, economic, medical or political grounds, to restrict or eliminate their use. 3. Currently, regular daily consumption of behaviorally-active doses (e.g., ›80% of adults in the United States) is widespread throughout the world; the extent of caffeine usage far exceeds that estimated for alcohol and nicotine which rank second and third, respectively, as the most widely consumed psychotropic drugs worldwide. 4. Habitual consumption of behaviorally active doses of caffeine occurs in widely different vehicles (e.g., drinking of coffee, tea, maté; chewing kola nuts) and under widely different social and cultural conditions; thus, caffeine ingestion is a remarkably generalized form of drug self--administration occurring across a broad range of dietary and contextual conditions.

Although the health risks associated with caffeine use are minor relative to the life-threatening health-risks associated with classic drugs of abuse such as cocaine, caffeine is, nonetheless, a useful model compound for drug abuse research to investigate pharmacological and behavioral mechanisms by which such drugs come to capture and control human drug-taking behavior. The remainder of this abstract reviews an emerging research literature on caffeine as it relates to our understanding of self-administered and abused substances.

Role of Adenosine, Doparnine and Cholinergic Systems in the Central Action of Caffeine: The behavioral effects of caffeine appear to be due in large measure to antagonism of the action of endogenous adenosine at A_1- and A_{2a}-receptors in the central nervous system. Other possible mechanisms of action of caffeine, such as release of intracellular calcium, inhibition of phosphodiesterases and blockade of regulatory sites on GABAA-receptors, would likely require much higher concentrations than the micromolar concentrations of caffeine associated with behavioral stimulation. Chronic blockade of adenosine receptors by caffeine would be expected to result in alterations in the central receptors and pathways that are regulated by adenosine through A_1-and A_{2a}-receptors. Indeed, chronic caffeine does after the density not only of adenosine receptors, but also of adrenergic, cholinergic, GABAergic and serotonergic receptors. Remarkably, dopamine receptors seem unaltered, although it seems clear that the behavioraI effects of caffeine are closely related to alterations in dopaminergic function. Behavioral responses to agents acting through adenosine, dopaminergic and cholinergic pathways are altered. Indeed, tolerance to behavioral effects of caffeine has been reported to be accompanied by tolerance to selective D_1- and D_2-dopaminergic agonists, but remarkably not to combinations of D_1- and D_2-agonists. Selective adenosine agonists and antagonists have provided some further insights into central roles for adenosine receptor subtypes that are affected by caffeine and other xanthines. Thus, behavioral stimulation by xanthines appears to require blockade of both A_1- and A_{2a}-receptors. Chronic treatment with theophylline results in alterations in central levels of adenosine and other receptors similar to those caused by caffeine. In contrast, chronic theobromine and isobutyl methylxanthine cause alterations only in A_1-adenosine receptors. Chronic and acute treatment with adenosine analogs or xanthines often have diametrically opposite effects on cognitive functions and neuroprotection. As yet, a coherent explanation of the acute and chronic effects of caffeine in terms of blockade of adenosine receptors has not emerged. Interactions between pathways subserved by A_1- and A_{2a}-adenosine receptors complicate attempts to interpret caffeine pharmacology, as does the complex control by adenosine receptors of dopruninergic, cholinergic and other central pathways.

Preclinical Studies of Behavioral Effects of Caffeine Relevant to Potential for Abuse: In humans, low doses of caffeine increase wakefulness and can produce positive mood states similar to those engendered by low doses of nonxanthine psychomotor stimulants, such as amphetamine. These effects may be related to the reinforcing effects which maintain consumption of caffeine. In contrast, high doses of caffeine are more likely to produce negative mood states which might serve to limit drug intake by many individuals. Caffeine has biphasic effects on the behavior of laboratory animals that appear to be relevant to the effects of low and high doses of caffeine in humans and to potential for abuse. For example, like nonxanthine psychomotor stimulants in the rat, low to intermediate doses of caffeine (*i.e.,* 1.0-30 mg/kg) increase locomotor activity, condition a place preference, produce discriminative stimulus effects that have commonalities with those of amphetamine-like drugs, and stimulate rotational behavior following unilateral lesion of the nigrostriatal tract. Caffeine is a competitive antagonist at adenosine receptors, an action that is closely associated with its behavioral stimulant effects; it may enhance dopaminergically mediated neurotransmission secondarily to adenosine receptor blockade, providing a basis for the effects that low caffeine doses have in common with amphetamine-like drugs. On the other hand, intermediate to high doses of caffeine (*i.e.,* 30-100 mg/kg) elevate the reinforcement threshold for intracranial electrical self-stimulation (ICSS), condition a place aversion, and produce discriminative stimulus effects that have no commonalities with those of nonxanthine psychomotor stimulants. These high-dose effects of caffeine appear to be relevant to the negative mood states induced by higher doses of caffeine in humans. However, little is known about mechanism of action or how the high-dose effects of caffeine might limit the behavioral effects of lower doses.

With daily drug administration, tolerance develops to many of the behavioral effects of caffeine, particularly those produced by low doses. Tolerance is pharmacologically specific, with cross-tolerance extending to other methylxanthine adenosine antagonists (*e.g.,* theophylline) but not to amphetamine-like psychomotor stimulants. There probably are multiple mechanisms that underlie caffeine tolerance, given the many actions of this drug. Behavioral and neurochemical evidence suggest that functional down-regulation of dopaminergically-mediated neurotransmission is the mechanism of tolerance to caffeine-induced stimulation of locomotor activity. Absence of tolerance to potentiative interactions that result from concurrent activation of the dopamine D_1- and D_2-families of receptors offers an explanation for the lack of cross-tolerance to nonxanthine psychomotor stimulants, which can activate concurrently multiple subtypes of the dopamine receptor. Rats, like humans, can become physically dependent upon caffeine: upon termination of drug administration there are changes in behavior that are opposite in direction to those produced by acute administration of caffeine (*e.g.,* decreased locomotor activity and decreased reinforcement threshold for brain stimulalion). Physical dependence upon caffeine in animals has not been characterized sufficiently to know if the phenomenon is an effect exclusive to low or high doses, or occurs with both.

Human Studies of Caffeine Subjective/Discriminative Effects and Reinforcement: At doses of 25-100 mg, caffeine is discriminable and produces positive self-reports such as increased alertness, desire to talk, energy and motivation to work. At doses > 200 mg, caffeine produces reports of anxiety, dysphoria and jitteriness. Most people can acquire discrimination of moderate to high doses of caffeine (100-320 mg), many can acquire a discrimination of lower doses (56 mg), and a few can learn to discriminate very low doses (10-18 mg). Discrimination of high doses (320 mg) is associated with negative subjective effects in contrast to the discrimination of low doses (< 178 mg) which is associated with positive subjective effects. Subjective and discriminative effects occur in the presence and absence of physical dependence and when subjects do not know caffeine is the drug being studied.

Reliable caffeine reinforcement has been demonstrated across different age groups, doses, methods, populations, vehicles and in the presence/absence of physical dependence. Reliable caffeine reinforcement occurs in 25-100% of subjects, depending on the above factors. Caffeine reinforcement is observed when tested at commonly consumed doses (25-100 mg/serving) and in ecologically valid settings (e.g., outpatient studies of soft drink consumption). Caffeine reinforcement is more likely to occur in subjects who are in environments that reinforce behaviors requiring alertness, in subjects who report stimulant effects from caffeine, and in subjects who report withdrawal headaches, fatigue and drowsiness.

Human Studies of Caffeine Physical Dependence: Physical dependence is manifested by time-limited physiological and behavioral disruptions (*i.e.,* a withdrawal syndrome) upon termination of chronic

drug administration. Recent studies have demonstrated that the incidence of caffeine withdrawal is higher, the daily dose level at which withdrawal occurs is lower, and the range of symptoms experienced is broader than previously recognized. Headache and fatigue are the most frequent withdrawal symptoms, with a variety of other symptoms occurring at lower frequency (*e.g.,* increased work difficulty, impaired psychomotor performance, nausea/vomiting). When caffeine withdrawal occurs, severity can vary from mild to extreme. The severity of caffeine withdrawal is an increasing function of caffeine maintenance dose and significant withdrawal symptoms have been observed when subjects were maintained on as little as 100 mg caffeine each day. Recent parametric studies have shown that caffeine withdrawal can be suppressed by the administration of doses lower than the maintenance dose and that increasing the duration of caffeine exposure produces greater caffeine withdrawal. The probability of caffeine withdrawal is an increasing function of caffeine maintenance dose. Studies indicate 25-50% of caffeine consumers in the general population report headache if they abruptly stop caffeine consumption. The withdrawal syndrome has an orderly time-course, with onset at 12-36 h, peak at 20-48 h, and duration usually ranging between two days to one week. There is increasing evidence that physical dependence may potentiate the rci nforcing cffects of caffeine.

Clinical Evidence for the Caffeine Dependence Syndrome: A clinical syndrome of drug dependence generally consists of several features associated with the pathologic use of a substance, which can include, but is not limited lo, aspects of physical dependence. Two recent studies have provided evidence that caffeine can produce a clinical syndrome of dependence. The first study, which was conducted at the University of Vermont, consisted of a telephone survey of 202 randomly-selected residents of Vermont. Participants were interviewed over the telephone about their caffeine use, using the nine generic DSM-III-R criteria for Psychoactive Substance Dependence as applied to caffeine. One hundred sixty-six of the 202 subjects reported current caffeine use, and in the previous year 27% of these 166 fulfilled criteria for a diagnosis of mild Caffeine Dependence (3-4 criteria), 14% had moderate dependence (5-6 criteria), and 3% had severe dependence (7-9 criteria). The most common symptom of Dependence was a persistent desire or one or more unsuccessful efforts to cut down or control caffeine use (reported by 51%).

In a study conducted at Johns Hopkins, subjects self-identified as having problematic caffeine use were assessed using a semi-structured clinical interview, the Structured Clinical Interview for DSM (SCID), modified to include a section diagnosing Caffeine Dependence. This diagnosis was based upon four of the seven generic dependence criteria used in DSM-IV. Sixteen subjects were found who fulfilled the criteria for a diagnosis of Caffeine Dependence. Ninety-four percent of the subjects fulfilled criterion #2 (withdrawal), 94% fulfilled criterion #7 (use continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance use), 81% fulfilled criterion #4 (persistent desire or unsuccessful efforts to cut down or control substance use), and 75% fulfilled criterion #1 (tolerance). The study employed a double-blind caffeine withdrawal assessment, in order to validate the presence of the withdrawal criterion (one of the four criteria used to make the diagnosis of Dependence). Eleven of the 16 subjects participated in this withdrawal assessment, and nine (82%) showed evidence of caffeine withdrawal, including eight with functional impairment.

The subjects in this study also were assessed for other psychiatric diagnoses besides Caffeine Dependence. While there were few concurrent psychiatric disorders in this population, there were high rates of past psychiatric disorders. Interestingly, the most common psychiatric disorders in remission were other substance use disorders (63%, 10 subjects), with the most prevalent drug class being alcohol (nine of the ten subjects).

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ELECTROPHYSICAL ANALYSES OF PSYCHOSTIMULANT DRUG ACTIONS: FROM THE SLICE TO THE AWAKE ANIMAL

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Cocaine and the 5-HT Connection in Slices of the Ventral Tegmental Area. J. T. Williams, D. L. Cameron and A. Bonci

Changes in the activity of dopamine (DA) neurons in the ventral tegmental area (VTA) are thought to be important in the formation of addictive behaviors. Cocaine blocks all three monoamine transporters and can affect VTA DA neurons by blocking the reuptake of locally-released DA and serotonin (5-HT). Dopamine D_1 and $5\text{-}HT_{1D}$ receptors are found on the terminals of afferent γ-aminobutyric acid (GAB A) neurons that synapse on VTA DA neurons. The role of these receptors in the action of cocaine was investigated using intracellular recordings in a brain slice preparation. Synaptic potentials were generated in the slice and GABA-mediated inhibitory synaptic potentials (IPSPs) were identified. Stimulation of DA D_1 receptors selectively enhanced the $GABA_B$ IPSP and this effect was blocked by D_1 antagonists. When D_1 antagonists were applied. the amplitude of the IPSP was decreased suggesting that tonic D_1 receptor activation exists in the slice. Cocaine deceased the amplitude of the GABA, IPSP. This inhibition was mimicked by 5-HT, the 5-HT releasing agent fenfluramine as well as the $5\text{-}HT_{1D}$ agonist sumatriptan and was attenuated by the 5-HT antagonist metergoline and pre-incubation of the slice with the 5-HT depleting agent para-chloramphetamine. The results of this study suggest that DA and 5-HT have opposing roles in modulating GABA input into VTA DA neurons. The actions of cocaine on this interplay may have implications for understanding its addictive properties.

Cocaine Actions in Raphe-Amygdala Serotonin Systems *In Vivo* K. A. Cunningham, P. M. Callahan, E. J. Mah, R. T. Windh

Intravenous and iontophoretic cocaine potently and reversibly depresses the activity of 5-HT raphe neurons by increasing synaptic 5-HT which stimulates impulse-modulating $5\text{-}HT_{1A}$ autoreceptors on 5-HT cell bodies. Mesohabenular long-loop feedback circuits, which may include a DA D_1 component, also participate in the acute inhibitory effects of cocaine on 5-HT DR neurons. A chronic cocaine regimen which results in behavioral sensitization enhances autoregulatory $5\text{-}HT_{1A}$ processes possibly due to altered 5-HT transporter function. The amygdala is innervated by 5-HT (and catecholamine) neurons and may mediate some behavioral effects of cocaine. We have found that depletion of 5-HT with fenfluramine treatment (12 mg/kg), B. I. D., 4 days) increased the neural activity in amygdala suggesting that 5-HT normally provides inhibitory tone. Intravenous administration of cocaine inhibits cellular activity in most cells, although some neurons were excited (28%), and mixed responses were also observed (19%); only a few neurons were non-responsive (6%). In contrast, only suppression of cell firing was observed during iontophoresis with cocaine. In sensitized rats, subsensitivity to iontophoretic 5-HT was observed. Although the receptor subtype responsible for the inhibitory response to 5-HT has not yet been identified, this tolerance may be related to decreased amygdala $5\text{-}HT_{1A}$ receptors previously observed following this regimen of cocaine treatment. Acute cocaine has significant effects upon 5-HT systems while chronic cocaine results in adaptational responses of these circuits. Although the present research represents a focus on raphe-amygdala 5-HT circuits, there is also evidence to support cocaine-induced modifications in 5-HT function in other mesolimbic neurons and a clearer perspective with regard to the integration of these 5-HT changes with those that are observed in the DA system is required.

Cocaine Actions in Mesocorticolimbic Dopamine Systems: Role in Sensitization and Withdrawal. F. J. White

A series of experiments has been undertaken to determine the electrophysiological effect of psychomotor stimulant administration on the mesocorticolimbic DA system, as they relate to behavioral sensitization and

withdrawal. Twice daily cocaine administration for 14 days resulted in relatively persistent behavioral sensitization that was evident following a one, but not two, month withdrawal. Repeated cocaine also caused a transient subsensitivity of DA D_2 autoreceptor function within the VTA, and an increase in the basal activity of the VTA DA neurons. The latter effect may be a common mechanism underlying the initiation of sensitization to cocaine, amphetamine and morphine. It was also demonstrated that antagonists of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor prevented both behavioral sensitization and VTA DA autoreceptor subsensitivity. Moreover, increased sensitivity of VTA DA neurons to glutamate and to the non-MDA receptor agonist α–amino-3-hydroxy-5-mediyl-isoxazole-4-proprionate (AMPA) were observed following repeated cocaine (and amphetamine) treatment. These findings suggest that glutamate receptors are required for the induction of stimulant sensitization and that plasticity of both glutamate and DA receptors may lead to enhanced activity of mesocorticolimbic DA systems.

At the primary termination of the mesocorticolimbic DA system, i.e., the nucleus accumbens (NAc), repeated administration of cocaine increased the sensitivity of DA D_1 receptors, an effect that persisted with a time course identical to that of behavioral sensitization. In addition, there was a dramatic decrease in the excitability of NAc neurons, demonstrated both with respect to glutamate-induced excitation (via both NMDA and AMPA receptors) and action potential generation evoked by intracellular current injection. Additional intracellular recordings indicated a reduction in the amplitude of action potential after repeated cocaine, perhaps indicating phosphorylation of voltage-dependent sodium channels. These findings suggest that the expression of sensitization is correlated with a reduction in the excitability of NAc neurons. Additional experiments with repeated administration agonists exhibiting selectivity for either DA D_1-class or D_2-class receptors, or their combination, indicated that a persistent sensitization to cocaine required the induction of both transient DA d_2 autoreceptor subsensitivity within the VTA, and persistent DA D_1 receptor supersensitivity within the NAc.

Neural Activity During Cocaine Self-Administration in the Awake Rat: A Comparison with Food and Water Reward. J. M. Paris

The ventral striatum appears to be responsible for the detention, maintenance and anticipation of reinforcement by both appetitive stimuli and abused drugs. We hypothesize that the neural signals which encode drug or appetitive stimuli seeking behavior differ for each reinforcer. The VTA is also critical brain region subserving the reinforcing properties of a variety of stimuli such as food, waler, and cocaine. Previous studies have shown that DA and non-DA VTA neurons encode information specific to one or more behavioral events within the response-reinforcement continuum. In particular, DA neurons appear to be more responsible for detecting the presentation or consumption of a reward during the early learning phase when an organism is recognizing that a stimulus is rewarding.

Although a great deal has been done to understand how cocaine affects this system, little attention has been paid to: 1) the electrophysiological basis underlying its reinforcing effects in awake subjects and, 2) how responses associated with one reinforcer may be related to those associated with other rewarding stimuli. The purpose of our current studies is to determine how neurons in the VTA-nucleus accumbens circuit alter their neuronal activity before and after an operant response which leads to presentation of one of three reinforcers: food, water and an intravenous injection of cocaine. The results thus far indicate that there are distinct patterns of neuronal firing associated with each reinforcer. Most VTA neurons show phasic patterns of tiring (increase, decrease or biphasic changes) following the delivery and during the consumption of the food and water reinforcement. In contrast to the NAc, there are very few neurons in the VTA which respond to cocaine reinforcement. The results substantiate the hypothesis that VTA-NAc neuronal activity is modulated by the behaviors within the

response-reinforcement cycle. Importantly, these alterations in phasic firing patterns appear to be *distinct* for a given type of reinforcer (food, water, cocaine). Further studies are necessary to identify specific VTA neuronal firing patterns which may encode cocaine self-administration and how information from various inputs to the brain reward pathway is integrated and processed.

Discharge Patterns of Nucleus Accumhens Neurons: Relationship to States of Arousal, Drug Self-Administration and Novel Stimuli. S. J. Henriksen

In order to investigate the cellular substrate of these behavioral events we have recorded from identified NAc neurons in unanesthetized, freely-moving rats and have attempted to correlate their discharge with on-going behaviors, state changes, alcohol administration as well as episodes of heroin and cocaine self-administration. Single accumbens neurons were recorded with nichrome micro-wires assembled in a moveable microdrive. With this configuration we have been able to record the firing patterns of over 200 NAc neurons for up to several hours. The rate of firing of these neurons declines during transition to slow-wave sleep while they have their highest relative discharge rates in REM sleep a theta-related state. In an open field behavioral chamber, NAc neurons respond lo prolonged nosepoking events lasting from 10 to 50 sec by a decrease in spontaneous activity. Immediately prior to nasal entry into a hole, the firing rate of most cells can be briefly elevated above baseline. Similarly, some neurons in the NAc repeatedly decrease their discharge rate during focused attention behavior, and during ingestion to a favorite novel food morsel (popcorn). We have also earlier reported that NAc neuronal discharge in anesthetized rats is inhibited by systemic acute, non-contingent, heroin treatment aND this effect is reversed by naloxone. However, our current studies in freely-moving rats suggest that only about 25% of NAc neurons encountered are inhibited during heroin (0.06 mg/kg/injection) self-administration behavior. We also observed that decreases of NAc neuromaI activity were antagonized by co-administration of a mixture of naloxone extinction paradigms, heroin self-administration behavior can be reacquired by a short period of non-contingent heroin administration. Following re-acquisition, the NAc cellular responses mimic their pre-extinction pattern. In addition, parenteral administration of moderately intoxicating doses of ethanol (1.2-1.4 g/kg, *i.p.*) significantly reduced spontaneous NAc unit activity without altering spike amplitudes. SCH-23390 (120 µg/kg, *i.p.*), a selective $D\text{-}_1$ antagonist, also failed to reverse ethanol-induced inhibition of NAc neurons. Taken together, these data reinforce our earlier conclusions that the NAc is a heterogeneous neuronal assembly with diverse neuronal responses to behavioral contingencies and complex pharmacological responses to different class of abused drugs. The exact role of the NAc and related circuits in the self-administration of abused drugs remains to be elucidated.

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Available upon request from Kathryn A. Cunningham.

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CROSS-CULTURAL COMPARISON OF SUBSTANCE ABUSE: RESULTS FROM THE 12-SITE W.H.O. STUDY ON RELIABILITY AND VALIDITY

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The WHO Study on the Reliability and Validity of Substance Abuse Instruments (R/V Study) is a 12-cenler study (in 10 different countries) aiming lo test the reliability and validity of three diagnostic instruments used lo assess alcohol and other substance use disorders. The purpose of the R/V Study is to further develop the substance abuse sections of these instruments so that a range of substance-related diagnoses can be made in a systematic, consistent and accurate way.

Two of three instruments tested were developed by the WHO as part of the WHO/NIH Joint Project on Assessment and Classification of Mental and Alcohol- and Drug-Related Problems. These Joint Project instruments are the Composite International Diagnostic Instrument (CIDI) and Schedules for Clinical Assessment of Neuropsychiatry (SCAN). A third instrument, which is a specific alcohol and drug instrument, the Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS), was added in order lo test the Joint Project instruments against an independent measure which has been used extensively in large population surveys. AUDADIS has different ways of operationalizing the diagnostic criteria and has a different structure from the other two instruments, thus was thought to be an excellent comparison.

The CIDI and the AUDADIS are both highly structured interview schedules based on the diagnostic criteria of the ICD and DSM systems. Questions in the AUDADIS and CIDI are spelled out exactly and responses are recorded verbatim within pre-ordained categorical response options. Despite these similarities, the CIDI and AUDADIS differ markedly in wording of questions, interviewing structure and formatting of responses. In addition, the AUDADIS (like the SCAN but unlike the CIDI) includes precise questions about whether the dependence symptoms cluster within a limited time as required by both DSM-IV and ICD-10. Different than both the CIDI and AUDADIS, the SCAN is a semi-structured interview in which all ICD and DSM symptoms are listed, accompanied by careful definitions of each in a glossary. Suggested questions for each symptom are provided, but trained clinicians who administer the SCAN are expected to explore in detail the specific histories of the respondent lo ascertain whether each symptom is present or absent.

The R/V Study includes both one week test/retest studies of all three instruments as well as comparison studies in which two or three of the instruments were administered (on separate occasions and by different, blinded interviewers) to the same respondents. In addition, several other components were included: 1) debriefing questionnaires were administered after every interview to both the respondent and the interviewer; 2) the Discrepancy Interview Protocol (DIP) was administered after the final diagnostic interview with each respondent to query respondents about reasons for giving different responses to different interviews; and 3) an independent clinical evaluation was administered by expert clinicians to a sub-sample of respondents at all sites so that "expert" diagnoses could be compared with diagnoses obtained with the CIDI, SCAN and AUDADIS.

The 12 R/V study sites include Amsterdam, the Netherlands; Ankara, Turkey; Athens, Greece; Bangalore, India; Farmington, Connecticut, USA; Ibadan, Nigeria; Jebel, Romania; Luxembourg, Luxembourg; San Juan, Puerto Rico; St. Louis, Missouri, USA; and Sydney, Australia (two sites). Each site recruited approximately 150 subjects — at least 100 from general population or primary care settings and less than 50 from substance treatment facilities. Overall, the total sample is 1825 persons of whom 68% (n = 1241) are male and 23% (n = 420) are from treatment facilities. The mean age of the sample is 37.2 years.

TEST-RETEST RELIABILITY OF THE SUBSTANCE USE DISORDERS SECTIONS OF THE CIDI, SCAN, AND AUDADIS

Test/retest sub-studies were performed at seven sites. The CIDI test/retest sites were San Juan and Sydney; SCAN test/retest sites were Ankara and Farmington; and the AUDADIS test/retest sites were Bangalore, Jebel and Sydney. Initial analyses performed on the test/retest interviews included calculation of the *kappa* statistic to measure chance corrected agreement on diagnosis and diagnostic criteria. All three instruments showed excellent diagnostic agreement for opiate dependence. Agreemeut on other dependence diagnoses was generally good although reasonably precise estimates of agreement could only be calculated for alcohol, opiates, cannabis, sedatives, cocaine and amphetamines. Sample sizes for the other substances were inadequate to assess agreement precisely. The dependence criteria had similar levels of agreement as the overall diagnoses although the individual *kappas* varied somewhat. For DSM-IV Abuse and ICD-10 Harmful Use diagnoses, *kappas* were much lower, indicating much poorer agreement on these other diagnostic categories.

DSM-IV ITEM, CRITERION AND DIAGNOSTIC CONCORDANCE ACROSS AUDADIS, CIDI, AND SCAN ALCOHOL AND DRUG SECTIONS

As part of the R/V study, three sites were involved in a three-way comparison of diagnostic assessments — using the CIDI, SCAN and AUDADIS. This three-way comparison was conducted in Athens (n=148), Luxembourg (n=118) and St. Louis (n=151). The substances used most by the subjects were alcohol, cocaine, opiates and cannabis. The protocol for this study required that the sequence of the instruments would be varied and that the maximum time between interviews would be one week.

Of the 417 persons assessed, one-third were female. To study the concordance of DSM-IV criterion for the four most commonly used substances, kappas were calculated for each pair of instruments and for each of the diagnostic criteria: CIDI vs. SCAN; AUDADIS vs. SCAN and CIDI vs. AUDADIS. Testing the differences between kappas for each comparison was made with each instrument as the "gold standard". Results showed a high level of consistency between the non-clinical assessments (CIDI and AUDADIS) and the SCAN. The only differences appeared to be with cannabis dependence symptoms.

Reasons for discrepancies between the assessments were assessed with the Discrepancy Interview Protocol (DIP) — an evaluation for determining differences between answers to individual questions in three different interviews. This preliminary look at the data revealed that answers differed primarily because questions were different in the three instruments and because the respondents didn't understand the questions.

These results suggest several important issues for discussion: that methodologic work on comparisons of three assessments can be done with minimal attrition; that the reasons for discrepancies between interview responses do not differ much by culture; that the DIP can be used to help guide further revisions of the instruments to increase the reliability and validity of' responses; and that the assessments agree more than we might have expected.

CROSS-CULTURAL VARIABILITY IN ICD-10 AND DSM-IV SUBSTANCE DEPENDENCE SYNDROMES

Cross-cultural variation in diagnostic applicability could have a serious impact on diagnosis and thus on the replication of clinical research in different cultural settings. To examine the cross-cultural variability in substance dependence symptoms, data from the WHO/NIH international study were evaluated. To avoid discrepancies due to use of different instruments, data for this paper were limited to the SCAN because this instrument was used at more sites than any of the other instruments (eight sites, n = 1244).

Among dependent persons, the rates of endorsement of ICD-10 and DSM-IV dependence criteria were compared across the eight sites which administered the SCAN interview for the five most common substances: alcohol, cannabis, cocaine, opiates and sedatives. In addition to comparisons for the entire samples at each of the sites,

comparisons were also performed separately for men and women. Finally, the rates of diagnosis according to ICD-10 and DSM-IV dependence criteria were compared.

These preliminary analyses indicate that alcohol and cocaine dependence symptoms had remarkable consistency across all sites. That is, respondents endorsed dependence symptoms with approximately the same frequency at each and every site. For opiate and sedative dependence symptoms, general consistency was seen, with minor exceptions at two sites. For cannabis dependence greater variation was seen. When the consistency of symptom endorsement was examined for men and women separately, the number of women with dependence diagnoses was limited at several sites; thus the ability to compare men and women in their cross-cultural variability in dependence symptomatology was limited to a subset of sites. In general, it appeared that there was no more variation for women than for men in endorsement of dependence criteria. In addition, the symptom profiles of women and men did not differ significantly for any substance or site except for the symptoms of alcohol dependence at one site.

Comparing DSM-IV and ICD-10 diagnoses, greater variation was seen across sites in the DSM-IV syndromes than in the ICD-10. No statistical tests were performed on this data, but the consistency of the finding indicated a trend worth further investigation. The increase in variability of endorsement across sites of the DSM-IV compared to the ICD-10 criteria was seen in all live substances: alcohol, cannabis, cocaine, opiates and sedatives. Furthermore, for all substances, more persons were diagnosed dependent using the DSM-IV criteria than the ICD-10; for alcohol, cannabis and sedatives the difference reached statistical significance ($p < .05$) between dependence diagnoses according to DSM-IV and ICD-10 criteria.

These preliminary results support the validity of the dependence syndrome, with the possible exception of cannabis dependence, and supports the comparability of persons diagnosed with ICD-10 dependence in disparate settings. Men and women had little difference in symptom profiles and in cultural variation. Due to the apparently decreased symptom variability for ICD-10 dependence criteria compared to DSM-IV criteria, the ICD-10 criteria may be more appropriate for cross-cultural application than DSM-IV. This may be due to the more restrictive (and possibly homogenous) nature of the ICD-10 dependence syndrome as seen in the decreased number of persons diagnosed with dependence when using ICD-10 criteria. These differences will need to be assessed further with the final data set and using appropriate statistical techniques to control for differences in level of addiction and other potentially confounding variables. Nevertheless, these analyses generally support the consistency of the dependence syndromes in many different cultures and populations.

IMPLICATIONS FOR USE OF SUBSTANCE USE DISORDERS DIAGNOSTIC INSTRUMENTS IN PSYCHIATRIC AND SUBSTANCE ABUSE RESEARCH

The results of this study to date indicate a number of points applicable to research on psychiatric and substance use disorders. First, they illustrate that a large-scale study of this type can be conducted collaboratively across sites in several different countries. Second, the study indicates that a variety of different instruments and now available for research when diagnoses of alcohol and drug use disorders are needed. While each provides basic information on the occurrence of the diagnostic criteria for alcohol and drug dependence and abuse, each also provides slightly different additional information with regard to syndromal clustering of the criteria, their onset and their recency. Individual investigators can inspect all instruments and determine which one best fits the needs of a particular study. Third, the study presents evidence supporting the validity of the dependence syndrome concept (except in the case of cannabis), while indicating continuing problems with the conceptualization and operationalization of an abuse-like condition. Once the data analyses from this study are finalized and become available, considerably more information will be available to guide researchers in the options available in measurement of alcohol and drug use disorders. Using this study as a model, perhaps future research of a more substantive nature can also be conducted to investigate cross-cultural influences on aspects of alcohol and drug use disorders and their co-occurrence with other conditions.

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DOSE-DEPENDENT TRANSITIONS IN BEHAVIORAL RESPONDING AND ACCUMBENS CELL FIRING DURING COCAINE SELF-ADMINISTRATION

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Nucleus accumbens (NA) neurons exhibit a spontaneous transition in firing rates from activity unrelated to the cocaine reinforced response during the early portion of self-administration sessions, to one of four types of patterned discharges for the remainder of the session (Brain Res., 626:14-22, 1993; J. Neurosci., 14(2):7735-7746, 1994). The transition in NA activity corresponded with cessation of an initial burst of responding (termed load-up behavior) during the self-administration session to a stable lower rate. The relationship between transitions in behavioral responding and NA activity was examined further by: 1) varying the dose of cocaine (0.08, 0.16, 0.33, 0.50, or 0.66 mg/inf), or 2) pretreating animals 30 minutes prior to the start of the cocaine (0.33 mg/int) self-administration session with the dopamine D_1 receptor antagonist, SCH23390 (5 or 10 µg/kg, SC). NA neurons were recorded in 14 rats previously trained to press a lever (FR1) for intravenous infusion of cocaine (0.33 mg/inf over 5.8 sec). Results indicated that decreasing the dose of cocaine increased the number of load-up responses and similarly delayed the emergence of NA patterned discharges, in a dose-dependent manner. Likewise, pretreatment with SCH23390 prolonged the transitions in behavioral responding and NA activity, similar to decreasing the dose of cocaine. These findings indicate that transitions in behavioral responding and NA activity may be dependent upon achievement of a crucial level of systemic cocaine (and NA dopamine) during cocaine self-administration sessions in rats.

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THE STIMULUS CONTROL OF DRUG ABUSE: ADDITIVE SUMMATION OF COCAINE SELF-ADMINISTRATION IN RATS

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The effects of presenting independently-established discriminative stimuli in compound have been well documented for behavior maintained by conventional reinforcers (food, waler, shock avoidance). One such effect is known as additive summation, where a compound discriminative stimulus substantially increases behavior compared its elements. To determine whether drug self-administration is subject to additive summation, four rats were trained on a schedule (multiple VR5 VR5 extinction) where cocaine (iv, 0.17 mg/kg/infusion) was only available when either a tone or a light was present. Once the tone and light had been individually established as discriminative stimuli, they were presented together in a stimulus-compounding test performed in extinction (*i.e.,* with no drug delivered). The tone+light compound produced response rates (mean=15.6 responses/minute) significantly higher than those in either tone (4.7 R/min) or light (5.0 R/min) alone. Following this test, three rats were returned to baseline, then retested under maintenance conditions with an FR3 schedule in effect. The compound stimulus significantly increased rates of drug intake (Mean= 2.3 infusions/minute) compared to tone (1.3 inf/min) and light (1.1 inf/min). In a truly-random control group (N= 4), the compound stimulus produced response rates about equal to those in tone and light alone, demonstrating that the additive summation effect is associative in nature. In contrast, when these rats were switched to the multiple schedule, they showed additive summation (Compound: 14.6 R/min; Tone: 5.0 R/min; Light: 6.3 R/min) comparable to that of the first group. These results further confirm that general-process learning theory applies to drug reinforcers. because the same conditions are necnssary for additive summation of responding maintained by drugs and conventional reinforcers. The demonstration of 300% increases in drug seeking (extinction test) and 200% increases in intake (maintenance test) in this animal model suggests that combinations of environmental stimuli might substantially increase human drug use under similar conditions.

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ORALLY-DELIVERED COCAINE AS A REINFORCER: CHOICE BETWEEN DIFFERENT CONCURRENTLY-AVAILABLE DOSES

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The relative reinforcing effects of different doses of orally-delivered cocaine were examined in experiments with rhesus monkeys as subjects. Responding was measured during daily three hour sessions under fixed-ratio and lixed-interval schedules of reinforcement. Changes in experimental conditions (e.g., changes in the available cocaine dose) were made following six stable sessions. Initially, a wide range of cocaine doses (0.05, 0.2 and 0.8 mg/ml) was tested sequentially with water concurrently available. Under these conditions the rate of responding maintained by the cocaine solution exceeded water responding and was either: (a) an inverted-U shaped function or (b) a descending linear function of the available dose. Low or medium doses maintained more responding than the highest dose. However, when pairs of different cocaine doses then were made available concurrently (0.05 vs. 0.2, 0.05 vs. 0.8, 0.2 vs. 0.8 mg/ml), the higher dose consistently maintained more responding than the lower dose. Thus, response rate observed when doses were presented sequentially with water concurrently available did not always predict which doses would maintain the most responding when two different drug doses were concurrenlly available. In the concurrent choice tests, doses on the descending limb of the inverted-U shaped dose-response function (obtained when the doses were tested sequentially) were preferred to doses on the peak or on the ascending limb. These results indicate that the relative reinforcing effects of cocaine increase with increases in the magnitude of the drug dose.

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ESTABLISHING INTRAVENOUS SELF-ADMINISTRATION OF COCAINE UNDER SECOND-ORDER SCHEDULES IN RODENTS

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Most of the current intravenous drug-self administration experiments performed in rodents have used simple schedules of reinforcement; rats arc required to emit a fixed number of responses which produces an injection of drug (fixed ratio, FR). In monkeys however, it is possible to train subjects to work not just for the drug, but also for drug-paired stimuli (*e.g.,* tone). The present experiments sought to establish self-administration of cocaine under second-order schedules. Male Sprague Dawley rats were trained to nose-poke for injections of cocaine (0.66 mg/kg/inj) under an FR schedule. Each drug injection produced a two second tone. Once rats attained stable responding under an FR-3, they were switched to a second-order schedule, in which every third nose-poke during a three minute variable interval produced a two second tone; the first three responses completed after the interval produced both the tone and an intravenous injection of cocaine. High rates of responding (~ 2.5 resp/min) were observed in a group (n=4) maintained under a VI three minute (FR 3:S) with a two sec tone as the secondary stimulus. However, when the brief tones were omitted, but cocaine was still injected, response rates did not change. When saline injections were substituted for cocaine injections, but the brief stimulus tone was still presented, responding decreased within three sessions. This decrease, however, was no different from conditions when both the drug and secondary stimulus were omitted. Similar observations were made in another group of animals (n=4), when the second-order schedule was FI three minutes (FR 3:S) with a two second tone as the secondary stimulus. Changing the external conditioning stimulus to a two second period of light oscillation (5 Hz), also failed to demonstrate second-order control in rats (n=4). In contrast, rats working under a FR 5 (FR 10: S) second-order schedule showed decreases in response rates when the brief stimulus light was omitted. These findings demonstrate that behaviour maintained by a secondary stimulus can be established, but only under certain conditions.

OPTIMAL CATHETER PARAMETERS FOR INTRAVENOUS DRUG DELIVERY IN THE RAT

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Minimal systematic research has been conducted on factors affecting venous catheter patency in rats, despite the relatively short catheter life experienced by many laboratories. This project has systematically varied catheter design and catheter placement. Blood withdrawal patency was assessed on a daily basis as the primary dependent variable. Results indicate that blood can be withdrawn in most rats for at least 90 days when optimal parameters are employed. The most critical parameter is the placement of the catheter tip; immediately outside the atrium is optimal. In adult male Sprague-Dawley rats, this corresponds to inserting the catheter 32 mm, with the catheter entering the right jugular vein 5 mm from the pectoral muscle. All catheters were made of silicone rubber. The data show that the optimal tubing size is 0.025 i.d. x .047" o.d., and that rounding the tip by dipping the tubing in silicone elastomer promotes longevity.

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CHOICE BETWEEN COCAINE AND FOOD IN A DISCRETE-TRIALS PROCEDURE IN THE RHESUS MONKEY: A UNIT PRICE ANALYSIS

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The unit price (UP) model of drug consumption defines UP as the ratio of the instrumental requirement (IR) to the dose of drug. As UP increases, consumption is predicted to decreaze. Additionally, it is predicted that consumption at any given UP will be constant, regardless of the values of IR and dose that it encompasses. We tested these predictions in a discrete-trials choice procedure using rhesus monkeys (n=4) that choose between banana pellets and i.v. cocaine. Cocaine was available at FRs ranging from 2 to 1200, and doses of 0.05, 0.1, 0.2, or 0.4 mg/kg. Banana pellets were available at a constant FR of 30 for three one-gram pellets. Experimental sessions had 20 trials separated by 30 minute timeouts. Behavior in a condition was considered stable when an animal had three consecutive sessions in which the number of cocaine trials was within + 15% of the three-day mean, and a minimum number of sessions (5-8) had been run in that condition. Data within each dose were consistent with the prediction that consumption would decline as UP increased. However, when compared across doses there was little support for the prediction that consumption would be constant at a given UP. Instead, consumption was generally higher at higher doses. The data reveal limitations on the generality of the UP model.

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COCAINE-REINFORCED BEHAVIOR IN RHESUS MONKEYS: EFFECTS OF FEEDING CONDITIONS

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Cocaine served as a reinforcer for four rhesus monkeys as evidenced by greater cocaine than vehicle maintained responding under concurrent fixed-ratio schedules of oral cocaine or vehicle access. Monkeys were maintained at 80% of their free feeding weight. Monkeys had access to 0.8 mg/ml cocaine and vehicle under a concurrent FR 8. The ratio value was doubled across days until responding no longer persisted. A retest at FR 8 was completed and then the cocaine concentration was halved over days until responding no longer persisted. A retest at FR 8, 0.8 mg/ml cocaine was completed. The monkeys' food allotment was increased by 5 gm/day until food was left (*i.e.,* free access). The cocaine concentration response curve was reestablished. After a retest at FR 8 and 0.8 mg/ml cocaine, the ratio value was doubled as above. Typically, as the cocaine concentration was reduced responding persisted at lower concentrations under food restricted conditions. Under conditions of access to 0.8 mg/ml cocaine and increasing FR value there was little difference between food restricted and free feeding conditions. A behavioral economic analysis revealed that the demand curve had similar asymptotic values but was right shifted as unit price increased. These data are consistent with other data that show food restriction increases the reinforcing effects of drugs especially at higher unit prices.

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GENOTYPIC DIFFERENCES IN COCAINE SELF-ADMINISTRATION

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This study determined if different strains of rats show different patterns of i.v. cocaine self-administration under a progressive-ratio schedule (PR), because responses emitted under a PR schedule are thought to reflect the relative motivational eflicacy of a reinforcer. Inbred strains of rats, Fischer 344 (n=12), Brown Norway (n=13) and ACI (n=12), were subjects because restriction fragment length polymorphisms (RFLPís) have been identified that genotypically distinguish between these strains at dopamine D2 and D4 receptor loci, and the variance in RFLPs may be associated with an interrelated change in the reinforcing efficacy of cocaine in these animals. Rats were assessed for acquisition and stability of cocaine self-administration under the PR schedule for 40 daily sessions. Subsequently, a dose-effect curve for cocaine, 0.1, 0.3 and 0.9 mg/kg/injection, was determined. The effect of SCH 23390 (0.1 mg/kg) and eticlopride (0.032 mg/kg) pre-treatment were also tested against the same three doses of cocaine. Fisher 344s maintained significantly higher average breaking points (18.14 (0.11) than did the ACI (11.97 (0.93) and Brown Norway (14.3 (0.12) strains. For the training dose of cocaine (0.9 mg/kg/injection), the time of the average pause in responding that followed each injection was significantly shorter in Fischer rats (0.41 + 0.28 min) than rats of Brown Norway or ACI strains (1.80 + 0.75 min or 3.38 + 1.13 min respectively). Strain differences for full dose-effect curves were also significant, and Fischer rats still had the highest breaking point for all doses of cocaine ($p<0.01$). SCH 23390 and eticlopride significantly reduced the breaking points of the three doses of cocaine among the three strains ($p<0.01$). However, the degree of reduction was not significantly different across the strains. These data are consistent with the hypothesis that genotype is a significant determinant of the reinforcing efficacy of cocaine, although the variance of RFLPs at dopamine D2 and D4 receptor loci may not be the major factor.

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NON-SELECTIVE EFFECTS OF CCK ON FOOD AND COCAINE MAINTAINED RESPONDING IN RHESUS MONKEYS

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CCK is a neuropeptide that reduces food intake when administered peripherally. When delivered centrally, it has been shown to modulate dopaminergic activity in the nucleus accumbens, a site that has been proposed to play a critical role in drug-self-administration. In order to assess its involvement in the abuse potential of cocaine, the effects of CCK were compared on FR 30 responding maintained by food and different unit doses of i.v. cocaine (10-100 µg/kg/inj) in four monkeys. CCK decreased food intake in a dose-related manner, regardless of the unit dose of cocaine. However, the effects of CCK on cocaine intake depended upon the unit dose of cocaine. When responding was maintained by 10 µg/kg/inj, CCK decreased drug intake at doses similar to those decreasing food intake. When responding was maintained by 30 µtg/kg/inj, CCK decreased food and cocaine intake in a similar manner in two monkeys, and had little or no effect on cocaine intake in two other monkeys. When responding was maintained by 100 µg/kg/inj, the effects of CCK on cocaine intake were generally smaller than those on food intake. These results show that peripherally administered CCK can suppress cocaine self-administration in rhesus monkeys, and this effect appeared to depend upon the unit dose of cocaine. Thus, responding maintained by higher doses of cocaine may be more resistant to the effects of CCK. The behavioral effects of centrally administered CCK on cocaine self-administration in rhesus monkeys have yet to be determined.

BACLOFEN ATTENUATES THE REINFORCING EFFECTS OF COCAINE IN RATS

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The effect of the $GABA_B$ agonist baclofen on cocaine reinforcement was examined. In the first study, rats were trained to self-administer cocaine on a progressive ratio schedule. The response requirements for each injection during the session escalated according to the series: 1,2,4,6,9,12,15,20.25... The number of injections self-administered before responding ceased was defined as the breaking point (BP). Pretreatment with baclofen (2.5 mg/kg) reduced BPs across a series of unit injection doses of cocaine (0.18, 0.38. 0.75, 1.5 mg/kg/inj). Baclofen had no effect on responding for food reinforcement on an identical PR schedule. In a second study, rats were trained to self-administer cocaine on a discrete trials schedule. Animals were given the opportunity to respond for a single injection of cocaine (1.5 mg/kg/inj) during a ten minute trial. Discrete trials began at 30 min intervals continually for two weeks. Baclofen pretreatment (2.5 mg/kg) reduced daily intake by 33%. These data suggest that baclofen should be considered as a possible pharmacotherapy for cocaine addiction.

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OLAZEPINE DECREASES, WHILE CLOZAPINE INCREASES, THE REINFORCING EFFECTS OF SELF-ADMINISTERED COCAINE

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Previously, we have shown that clozapine, an atypical neuroleptic, reduces the rate of responding for cocaine on a fixed-ratio schedule and increases the breaking-point (BP) on a progressive ratio (PR) schedule of reinforcement. The present study was aimed at investigating the generality of the clozapine effect across a range of cocaine doses, and at investigating the effects of another alleged atypical neuroleptic, olanzapine, on cocaine self-administration. Rats were trained to self-administer each of four doses of cocaine (0.19,0.38,0.75, and 1.5 mg/kg/injecrion) on a PR schedule. The effects of olanzepine (n = 17) and clozapine (n = 12) on the BP at each cocaine dose were studied. Olanzepine (1.25 and 2.5 mg/kg, IP) dose-dependently shifted die cocaine dose-response curve to the right, reducing BP at each dose of cocaine [ANOVAs revealed significant treatment effects ($p < .05$) at each dose of olanzepine]. In contrast, clozapine (10 mg/kg, IP) shifted the cocaine dose-response curve to the left, increasing the BP at each cocaine dose [significant treatment effect ($p < .05$)]. These results corroborate our previous findings and show that olanzapine decreases cocaine reinforcement.

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BUPRENORPHINE + NONDRUG REINFORCERS YIELD ADDITIVE EFFECT ON PCP AND SMOKED COCAINE SELF-ADMINISTRATION

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Six male rhesus monkeys were trained to respond for orally delivered phencyctidine (PCP) and saccharin (SACC) or water. They were given intramuscular (i.m.) injections of buprenorphine (BUP, 0.005 mg/kg) for five consecutive days at each of five fixed ratio (FR) schedules (4, 8, 16, 32, 64). BUP or SACC treatment alone lowered responding for PCP by 35 - 65% across the range of FRs. The combined effect of concurrent SACC and BUP treatment reduced PCP self-administration in an additive manner, 70 - 85% across the range of FRS.

Five other male rhesus monkeys were trained to respond for smoked cocaine base and orally delivered SACC or waler. Smoke deliveries were available under six FR values (64, 128, 256, 512, 1024, 2048), and liquid deliveries were available under FR 1. The monkeys were given i.m. injections of BUP (0.01 mg/kg) for five consecutive days on each FR value. SACC had little effect on cocaine base smoking, reducing it only 0 - 19% across the FR values. BUP reduced smoke deliveries 19 - 48%, and the BUP - SACC combination produced a greater reduction of 42 - 7 1% across the FR values.

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THE INTERACTION OF COCAINE AND PENTOBARBITAL ON SCHEDULE-CONTROLLED RESPONDING IN RATS

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Recently, we reported that doses of cocaine and alcohol that had no effect on schedule-controlled responding alone dramatically suppressed such responding when given in combination, producing a synergistic effect (Sobel and Riley, 1994). The present experiment adressed whether this synergistic interaction was specific to alcohol and cocaine by assessing the effect of pentobarbital (both alone and in combination with cocaine) within the same schedule-controlled preparation. Specifically, five female Long-Evans rats were trained to respond on an FR20 schedule for a water reinforcer. Sessions were five minutes in duration with four sessions occurring daily, each session preceded by a nine minute lime-out period. Subjects were then administered cumulative doses of cocaine or pentobarbital. Following this, subjects were injected with ineffective doses of cocaine (or pentobarbital) prior to further close-response assessments with the alternative drug. Individually, cocaine and pentobarbital produced dose-related decreases in responding. Unlike the synergistic interaction between cocaine and alcohol, however, pentobarbital (or cocaine) had no effect on or tended to block the suppressant effects of each other. These data suggest that the interaction between cocaine and alcohol is not a function of the combination of cocaine with a CNS depressant and that the cocaine/alcohol interaction may be a function of the specific metabolite, cocaethylene, resulting, from their concurrent administration.

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PREDICTION OF TREATMENT SUCCESS AMONG HOMELESS COCAINE ABUSERS

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Treatment success was investigated among homeless cocaine abusers who participated in a controlled study designed to assess the effectiveness of an enhanced day treatment plus abstinent contingent work therapy and housing program. Subjects (N = 131) were male (79.4%), African-American (96.2%), age (35.8 years), randomized to enhanced day treatment or usual care, and assessed at baseline and 2, 6, and 12 month follow-up points on alcohol and cocaine use and days homeless and employed. It was hypothesized that certain demographic, historical, and treatment variables would predict success in treatment as defined as improvement at follow-up in three out of four outcome indices listed above. Subjects who did not meet this criteria were defined as no success. Stepwise logistic regression was used to discriminate between success and no success groups. The significance level for entry and staying in the models was .30. At two months, successful treatment was predicted by enhanced day treatment, three or more treatment attempts, poor employment history, female gender, less depressed, younger age, and veteran status (sensitivity=56.8%, specificity=70.2%, overall rate correct=64.4%). At six months, predictor variables were enhanced day treatment, poor employment history, severe drug use, female gender, older age, and less depressed (sensitivity=35.5%, specificity=85.1%, overall rate correct=69.4%). At 12 months, predictor variables were high treatment intensity, poor employment history, few drug overdoses, three or more treatment attempts, less severe alcohol use, and male gender (sensitivity=50%, specificity=77.5%, overall rate correct=68.3%). This study identifies important predictors of treatment outcome for homeless cocaine abusers which can be explored in future research.

ADDICTION AND HOMELESSNESS SEVERITY OUTCOMES FROM A CONTROLLED STUDY OF DAY TREATMENT

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Day treatment/work therapy (DT) was compared to usual care (UC) for homeless cocaine abusers on outcomes of addiction and homeless severity at baseline, 2, 6, and 12 months. DT was hypothesized to show better outcomes, Consenting homeless, substance abusing subjects (n=176) were randomly assigned and assessed by "blind" interviewers. Addiction Severity Index (ASI) and Homelessness Severity Scale (HSS) data were examined using Multivariate Wilcoxon Wei-Lachin analyses across all assessment points. UC involved individual and group counseling one/week, vocational and housing referral. DT involved social skills training six hour/day for two months. Subjects were transported to and from shelters and provided lunch. DT subjects could work refurbishing housing, contingent on abstinence. Significant within group effects, baseline to 12 months were found in UC for ASI Alcohol, Drug, Social/Family, and Psychiatric median Composite Scores; similar effects in DT were found for Employment, Alcohol, Drug, Legal and Psychiatric Scores ($p \leq .05$). Median days homeless over the last 60 days was 57 days at baseline for both groups and increased to 60 days for UC and decreased to five days for DT. Differences between groups favoring DT on days homeless was significant ($p=0.026$). Homeless Severity Scale median scores (range) at baseline, 2, 6, 12 months were: for UC 13.36 (12.22), 13.28 (13.57). 13.00 (13.79, 13.00 (13.27); and for DT 13.15 (14.15), 13.00 (13.72), 7.00 (14.00), 7.44 (13.75). There was significant within group, improved homelessness severity only for DT: Paired Wilcoxon Tests for DT baseline to six months ($p<0.01$), to 12 months ($p<0.01$). Between group comparisons using Wilcoxon Test revealed greater reduction in homelessness severity for DT, at six months ($p<0.01$) and at 12 months ($p<0.05$). This appears to be the first demonstration homeless cocaine abusers can be retained in treatment and experience significant impacts on their Substance Use Disorders and homelessness severity.

EVALUATING ALTERNATIVE TREATMENTS FOR HOMELESS SUBSTANCE-ABUSING MEN: OUTCOMES AND PREDICTORS OF SUCCESS

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The present study was designed to explore the relative efficacy of three types of service delivery intervention models for homeless men with alcohol and/or drug problems, primary crack cocaine users: integrated comprehensive residential services provided at one site (Group 1); on-site shelter-based intensive case management with referrals to a community network of services (Group 2); and usual care shelter services with case management (Group 3). It was hypothesized that Group 1 would show better outcomes than Group 2, and that Group 2 would manifest better outcomes than Group 3. In addition to assessing the relative efficacy of these approaches in terms of drug and alcohol use, residential stability, economic and employment status, the project also sought to examine what personal factors best predicted successful outcomes for clients. A total of 722 clients were randomly assigned to the three treatment conditions, and then assessed at baseline and approximately six months following discharge. All three treatment groups improved significantly over time in terms of reduced alcohol and cocaine use, increased employment, and increased stable housing, but contrary to expectations, no differential improvement was found among groups. Successful outcomes were predicted by lower recent and lifetime substance use, fewer prior treatment episodes, more stable housing at baseline, fewer incarcerations, and less social isolation. Differentiations may need to be made during initial intake assessments of clients who may be particularly difficult to treat on the basis of greater lifetime and recent substance use patterns because of poor prognosis.

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THIRTEEN MONTH OUTCOMES OF DAY HOSPITAL VERSUS INPATIENT TREATMENTS FOR COCAINE DEPENDENCE

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We previously found few differences between day hospital (DH-n=85) versus inpatient (IP-n=67) treatments for cocaine in a male veteran, primarily African American study sample at four and seven months post-treatment entry. This presentation extends the analysis of outcome to 13 months. The findings revealed essentially no differences in the outcomes of the DH and IP groups at 13 months followup. As an example, 68% of the DH subjects reported being abstinent during the past 30 days compared to 66% of the IP subjects. 50% of the urine screens were positive for cocaine for the DH group, contrasted with 43% for the IP group.

In general, baseline and end of week one counselor ratings were relatively weak predictors of frequency of 13 month cocaine use; while measures more proximal to the 13 month followup evaluation were relatively strong predictors.

EFFECTIVENESS OF OUTPATIENT VERSUS DAY TREATMENT FOR COCAINE USERS

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Greater exposure to treatment has been positively related to successful treatment outcome. It is therefore expected that day treatment providing highly structured activity and clinical intervention for drug abusing patients over an extended period of time would be more likely to result in treatment success than would standard outpatient care. Samples of inner city cocaine users were randomly assigned to either day (40 hours per week) or standard outpatient (3 hours per week) treatment. Our findings reveal, however, that no differences in retention rates or cocaine use could be found between the two groups after one month in treatment and after the complete 12-week course of treatment. Living arrangements (structured shelter versus independent living situations) were found to be related to retention and cocaine use after one month for both samples of patients, however, with those in a structured setting more likely to remain in treatment and achieve cocaine abstinence. After 12 weeks, the relative effectiveness of the two treatments was not significantly different. In fact, outpatients tended to show longer durations of cocaine abstinence. These findings represent a challenge to the previous research regarding exposure to treatment, at least for this particular addict group. Possible explanations for these findings include: 1) the voucher incentive system was a powerful intervention overwhelming the effects of amount of treatment, 2) while the two interventions were identical in terms of individual counseling components they differed with respect to type and quantity of group interventions. These additional group components may not be effective. Indeed, they may be deleterious, due to increased negative peer influence developing in the day treatment setting. Further, participation in day treatment may limit the opportunities for patients to practice the skills required to maintain abstinence in the "real life" environment.

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CRAVING PRIOR TO ADMISSION IS CORRELATED WITH DECREASED TREATMENT RETENTION

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We measured depression and craving at intake for 38 working class, cocaine abusing patients in an ambulatory, fee-for-service drug treatment program. We hypothesized that these values would be predictive of length of stay in treatment. Thirty-two of the 38 subjects considered cocaine to be their primary drug of abuse. On admission, depression was measured using the Beck Depression Inventory (BDI), and craving was measured by patient response on two ten-centimeter visual analog craving scales, one for the past 24 hours and the other for the past week. Demographic information, drug use history, and admission or denial of withdrawal symptoms were also obtained by a self-report survey. Patients were divided into three groups: those who did not progress past the clinic's evaluation stage (ES, n=11) and were not accepted to the program, those who were accepted to the program but did not progress to the more advanced stage of treatment (short term, ST, n=15), and those who progressed to the more advanced stage of treatment (long term, LT, n=12) by maintaining abstinence for 30 days and attending eight weekly sessions. ST patients had significantly higher craving scores for the week prior to admission than LT patients ($p<.05$), but there was no significant difference in scores between ES and ST patients, and no significant difference between groups on the admission BDI. The three groups were not distinguished by demographic traits. A higher craving score for the past 24 hours correlated with a higher score on the BDI ($p<.005$) and with admission of feelings of withdrawal in the past 24 hours ($p<.05$). Our study was significant for a number of reasons. We looked at a population that is not often studied, working class, employed, ambulalory patients. High craving scores served as a predictor for earlier drop out and could be used as a screening device. Additionally, although we found a correlation between depression and craving, previous studies from our group found no correlation between these two assays when studying an inpatient population. This disparity merits further study.

THE SPANISH VERSION OF THE INDEX OF CORE SPIRITUAL EXPERIENCE (INSPIRIT) IN A SOUTHWEST U.S. LATIN0 POPULATION

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The Index of Core Spiritual Experience (INSPIRIT) was designed to" assess the degree of a spiritual experience and determine how the experience contributes to a personal well being." "It is the spiritual experience within the person that transcends and connects the personal self to a higher self." Research has suggested that a "spiritual experience" is similar to that of a drug induced "euphoric high." The INSPIRIT has been translated from English to Spanish in order to administer it to Latino people who only speak the Spanish language. The objective of this investigation was to perform an item analysis of the inventory's questions and assess it's cultural relevance for literate and Spanish speaking adults from the Houston area. The inventory was administered to a sample who were culturally representative of the group for whom it is ultimately intended to serve. Demographic data along with identified perceptual reactions to this inventory are presented. The information contributes to the validity, reliabilily, and normative data of the INSPIRIT.

COUNSELING AND SERVICES FOR COCAINE USE: FINDINGS FROM THE COCAINE TREATMENT OUTCOME STUDY (CTOS)

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The National Institute on Drug Abuse authorized the Cocaine Treatment Outcome Study (CTOS) as a companion study to the national Drug Abuse Treatment Outcome Study in order to provide accelerated information on the characteristics of cocaine-using clients and their co-occurring conditions, their treatment, and treatment outcomes. CTOS is a retrospective investigation of treatment outcomes for cocaine use in a sample of 23 programs representing three major modalities of treatment across seven U.S. cities, including three major study components: abstraction of clinic records, posttreatment face-to-face interviews with a sample of 772 former cocaine-using drug abuse treatment clients, and descriptive information on the programs serving these clients. Results indicate that after leaving the index treatment, approximately one-third of all clients received additional drug abuse treatment. Although clients reported problems in a variety of areas in addition to drug abuse in the year after leaving the index treatment, the level of services received during this period fell considerably below the level of reported need. These findings emphasize the need for a continuum of care in the year after treatment to include a full range of additional drug abuse treatment and services to support the cocaine user during the cycles of abstinence and use that often occur in the year following treatment. Also needed is a range of services to meet the needs that typically accompany cocaine use and its lifestyle.

COCAINE TREATMENT OUTCOMES FROM A NATIONAL MULTISITE STUDY: MULTIVARIATE EXPLANATORY MODELS OF OUTCOMES

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In response to the widespread use of cocaine by current and former drug abuse treatment clients, the National Institute on Drug Abuse sponsored an accelerated retrospective study of clients with a primary diagnosis of cocaine dependence. The purpose of the study was to determine outcomes for cocaine users during the first year after discharge. Subjects included 772 clients discharged from treatment across seven cities from 23 community-based treatment programs (nine long-term residential, five short-tenn inpatient, and nine outpatient drug-free programs). Initial descriptive and univariate analyses of treatment outcomes show (a) increases in reported abstinence from cocaine in the year after treatment; (b) declines across modalities in regular cocaine, marijuana, and heavy alcohol use from before to after treatment; and (c) declines in illegal acts to get money for drugs, suicidal ideation/attempts, and increased employmenl across all three treatment modalities. Client characteristics, time in treatment, planned lengths of stay, and reasons for entering and leaving treatment differed across modalities. Multivariate explanatory models were developed and are presented to show factors related to modality differences, retention, and positive treatment outcomes. The study provides evidence of, and support for, positive individual and societal outcomes for clients whose primary problem drug was cocaine. The outcomes include reduced substance use after treatment, greater employability/employment, fewer criminal and illegal acts, and declines in mental health impairments.

DEVELOPMENT OF COCAINE DEPENDENCE AMONG CLIENTS ENTERING FOUR MODALITIES FOR DRUG ABUSE TREATMENT

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This study examines sequencing of key drug-using events in the lives of cocaine-dependent individuals who entered a national sample of drug treatment programs from 1991 through 1993. The sequence of events indicated that the average age of first alcohol use was 13.8 years, with the first use of marijuana at 14.8 years, and first regular use (weekly or more often) of any illegal drug at 17.5 years. Cocaine use was initiated on average at 21.8 years of age, with regular use nearly three years later (24.5 years). problems related to dependence on cocaine began about one year after regular use. However, the first admission to a drug treatment program did not occur for another three years after such dependent-related problems began. The sequencing of events varied substantially for different birth cohorts. Of special note was the compression of events among younger clients entering treatment. Regression analysis was used to determine the most important factors related to the time from first use to development of problems. The strongest factor was birth cohort. Although the average time from first cocaine use to the development of problems was 3.8 years for all dependent clients, for those born in 1970 and after, the average time was about 1.5 years. For those born before 1950, the time was 6.3 years. In addition to birth cohort, which is related to the onset of the crack epidemic in the mid-1980s the most significant factors related to sequencing of events, age of alcohol initiation, client gender, age of first regular use of any illegal drug, and the presence of a history of suicidal thoughts or attempts are also significant factors that predict the length of time from first cocaine use to problem development.

DIFFERENCES BETWEEN COCAINE-DEPENDENT APPLICANTS FOR RESEARCH AND NON-RESEARCH TREATMENT

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The representation of research treatment samples has been questioned in several areas of medicine. We studied this in a sample of 131 applicants who met the DSM III-R criteria for cocaine dependence and were applying to non-research treatment (NRTx=50) or research treatment (RTx = 81) in two treatment centers in Baltimore. All subjects were administered the Addiction Severity Index (ASI). There were 89 (67.9%) males and 89 (70.1%) African-Americans. There was a trend (p=.055) for more females in the NRTx group. The NRTx group had significantly more medical, psychiatric, legal, and financial problems, and longer history of cocaine use. The NRTx group was also significantly less educated, less professionally skilled, had less stable living arrangements, and fewer support systems. These results show that there are medical and psychosocial difference between NRTx and RTx applicants. These differences may question the true representation of research treatment samples to the general population of cocaine dependent patients.

PRELIMINARY COMPARISON OF THREE VOUCHER SYSTEMS FOR COCAINE ABSTINENCE: DIMENSIONS TO CONSIDER

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We examined treatment outcomes of cocaine abusers earning vouchers for cocaine abstinence according to different voucher payment schedules. All subjects were scheduled to submit urine samples three times weekly and to attend the same schedule of individual cognitive-behavioral counseling and group training in interpersonal problem-solving. Subjects who earned vouchers could exchange them for goods and services that supported prosocial activities (*e.g.,* family activities, exercise, work or vocational training, independent living). We compared 65 subjects who did not earn vouchers (No Vouchers group), 63 subjects who earned vouchers for cocaine-negative urines on one payment schedule (Schedule 1), and 29 subjects who earned vouchers on another schedule (Schedule 2). Urinalysis results suggested that subjects earning vouchers on Schedule 2 achieved greater cocaine abstinence than subjects in the other two groups. In comparison to Schedule 1, Schedule 2 provided: 1) immediate consequences for each urine result, 2) greater reinforcer magnitude for initiating abstinence, 3) higher maximum earnings, and 4) increasing reinforcer intermittence with increasing abstinence. It did not provide: 5) a response-cost for cocaine positive urines or 6) differential reinforcement for sustained abstinence. We also present data from nine subjects in an pilot study replicating the schedule (Schedule3) used by Higgins *et. al.,* (1994) and Silverman *et al.,* (1995). Subjects receiving vouchers on Schedule 3 seemed to achieve longer abstinence than those on Schedule 1, but less than those on Schedule 2. We cannot draw conclusions about the relative efficacy of the three voucher systems, since we incorporated data from several studies. However, these data suggest that different schedules of voucher payment may produce different outcomes and systematic exploration of voucher payment schedules is warranted.

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MEASUREMENT OF COERCION TO DRUG TREATMENT

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We present a pilot study of a standardized interview scoring system for the detection and characterization of coercion to drug treatment in multiple psychosocial domains (family, social, legal, medical, financial, psychiatric/psychological, religious, and drug). Two hundred and sixty subjects in drug-free outpatient cocaine treatment were administered semi-structured interviews regarding perceived advantages-of-quitting and disadvantages-of-using cocaine, as well as reasons for seeking treatment at the present time. Responses were tabulated according to the presence or absence of "coercion" and "compulsion," and the primary operative psychosocial domain. "Coercive" responses 1) implied an escape or avoidance schedule of reinforcement, in which treatment entry was designed to terminate an aversive consequence of drug use; AND 2) occurred in an interpersonal context, in which another person or entity had the power to terminate the aversive consequence. "Compulsive" responses 1) implied a loss of choice or control concerning treatment entry; AND 2) occurred in an interpersonal context. "Noncoercive" responses EITHER 1) did not occur in an interpersonal context; AND/OR 2) contained a positive reinforcement schedule, in which treatment entry was designed to obtain positive contingencies; AND/OR 3) contained no discernible reinforcement schedule. Inter-rater reliability was exceptional over numerous scoring trials. Substantive analyses revealed that coercion is operative in multiple psychosocial domains, and that legal mandates exert substantially less influence over subjects' decisions to enter treatment than do informal social pressures; regardless of whether subjects were mandated to treatment by state government agencies (courts, probation, parole, child welfare services). Implications for drug treatment planning, relevant legal and ethical issues, and directions for future research are proposed.

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MEASURING MOTIVATION FOR CHANGE IN COCAINE ABUSERS

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Motivation for treatment or 'stage of change' has been cited as an important predictor variable in treatment outcome research. The efficacy of integrated treatment interventions may depend on applying the appropriate techniques at the right time. Action-oriented techniques may be more effective with individuals who are in the *derermination* or action stage of change, whereas individuals in the earlier stages might benefit more from insight-oriented treatments. Although substance abusers are hypothesized to progress cyclically through the five defined stages of change *(precontemplation, contemplation, action,* and *maintenance),* there has been little systematic evaluation of the change construct in this group. We have developed and evaluated a new motivation for change measure, the Motivation Assessment List for Cocaine (MAL-C), in 86 outpatient cocaine abusers. The MAL-C provides a rating of the subject's endorsement of each of the five stages of change and classification of subjects into a specific stage of change. Cronbach's alpha, Test-Re-test reliability, and predictive validity analyses indicate that the MAL-C provides reliable and valid motivation for change scores. These results suggest that the concept of motivation for change can be reliably measured among cocaine abusers. Preliminary stage of change profiles in our cocaine sample are consistent with the process of change theory. Classification of this population in terms of motivation for change may help to guide treatment interventions and provide useful information for treatment matching research.

TREATMENT READINESS IN COCAINE USERS

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We collected Stages of Change information from cocaine users (N=185) using a URICA based instrument, Processes of Change and Decisional Balance questionnaire data. Structural Equation Modeling was used to confirm the factor structure of these measures. This modeling supported the two factor model for the Decisional Balance scale, a three factor model of the Stages of Change in which the Action and Contemplation Scales were combined, but did not confirm the proposed four stage model; finally, the proposed factor structure for the Processes of Change did not hold, even when substantially modified. The major problem with the Processes of Change measure appeared to be the high intercorrelation among the scales; each scale was significantly correlated with every other scale. Individuals seeking treatment predominantly endorsed items consistent with these goals. Thus, over half these individuals had mean item endorsements of less than two (on a live point Likert scale with live being the highest level of endorsement) for the Pros of cocaine use, while over half had a mean endorsement score of four or more on the Cons of cocaine use. Similarly over half had a mean endorsement score of less than two on the Precontemplation scale, while over half had a mean eudorsement score equal to or greater than four on the Action-Contemplation scale. However, when scores on these scales in outpatients (n=141) were regressed on number of counseling sessions attended in a twelve week 26 session program separately for Pros and Cons, Stages, and Processes, none of these scales was impressively predictive. For instance, Stages only predicted 2.6% of the variance ($F(3,138)= 2.27$; $p=.083$). The other measures did worse ($p>.50$). These results along with the results of others indicate that these measures require further development before they can be fruitfully applied to illicit substance abusers.

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DEVELOPING MEASURES OF STAGES OF CHANGE FOR STIMULANT ABUSERS

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The Transtheoretical Mode1 of Behavior Change posits that intervention should fit one's stage of readiness for change. Conducting stage-matched interventions requires assessment of readiness to change. However, none of the current stage measures is designed specifically for stimulant users. We evaluated current measures (URICA - University of Rhode Island Change Assessment and Processes of Change questionnaires), and two new measures (a cartoon Stage of Change measure and a Goal Card Sort designed to measure Levels of Change) in interviews with 20 stimulant users recruited through outreach programs. Subjects completed the questionnaires and discussed items. Data were used to revise measures for further testing with a larger sample. The URICA and Processes of Change questionnaire contained vocabulary that was not understood, and subjects had difficulty remembering what they were to do throughout the lengthy Processes of Change questionnaire. Changes were made in the cartoons to address an observed lack of correspondence with URICA stage profiles. Goal Card Sort instructions were simplified to allow subjects to sort goals into "Stage of Change."

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PATIENT PERSPECTIVES ON THE PROCESS OF CHANGE IN SUBSTANCE ABUSE TREATMENT

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This study reports methadone patients' perspectives on the treatment they received for cocaine dependence (DSM-III-R criteria as measured by the SCID). Seventeen consecutive patients were selected from a larger sample cohort of cocaine-using methadone patients who were enrolled in a six-month cocaine treatment program (5 x individual/group sessions per week). The primary components of the program were cognitive-behavioral therapy (emphasizing positive reinforcement), relapse prevention, and therapeutic alliance. At treatment intake, subject reported using an average of 18 days in the past 30 days. Seventy percent had been using cocaine for at least the past five years and 70% reported no or failed previous treatment for cocaine use. Semi-structured interviews addressed patients' perceptions of the treatment process and personal change. Content analysis revealed nine themes that represented treatment process or outcome. Treatment efficacy was attributed to the therapeuric alliance, the use of structure and positive reinforcement, and the relapse pervention techniques. Patients reported improvements across several domains including cocaine use, coping skills and interpersonal relationships. Findings suggest that despite initial ambivalence, patients became highly engaged as a result of the positive reinforcement provided by the treatment, and that patients were able to effectively address psychodynamic issues within a cognitive behavioral format.

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MANUAL GUIDED INDIVIDUAL AND GROUP COGNITIVE BEHAVIORAL THERAPIES: SIMILARITIES AND DIFFERENCES

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Cognitive and behavioral techniques are widely employed in the treatment of drug abuse often concurrently in individual and group sessions. A manual-guided individual cognitive behavioral counseling package standardized for use in controlled studies of treatment of cocaine abusers was adapted for group. Some individual techniques were used unaltered, others were modified to enhance the critical therapeutic factor of group cohesion. When the frequencies of use of the techniques in individual counseling were compared to their use in group, six techniques were found to be more highly utilized. Two of them, cognitive rehearsal of cravings and delayed gratification were much better suited to group. Of the new techniques developed for the group, those most highly utilized were procedural in nature. Additional refinements were adopted including a stronger emphasis on self help aided by a take home member's handbook with brief explanations of the techniques. Blackboard use during group session, the use of two therapists and the presence of observers were additional innovations. The implementation of a group version of an individual manual is recommended as a way of refining an individual treatment package.

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VOUCHER-BASED REINFORCEMENT OF COCAINE ABSTINENCE: EFFECTS OF REINFORCEMENT SCHEDULE

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A schedule of voucher-based reinforcement involving escalating pay for sustained abstinence has been effective in treating cocaine abuse. Under this schedule, patients receive a voucher for each cocaine-free urine; vouchers have monetary values that increase with the number of consecutive cocaine-free urines. While this schedule has been effective for many patients, some patients have failed to achieve sustained abstinence. A modification of this schedule was tested in an effort to improve abstinence outcomes. Cocaine abusing methadone patients were randomly assigned to receive vouchers for 12 weeks under 1) an escalating pay schedule (n=20), 2) an escalating pay schedule with start-up bonuses (n=20), or 3) a noncontingent schedule (n=19). The start-up bonuses were designed to provide substantial immediate reinforcement for initiating abstinence. The contingent voucher interventions significantly increased subjects' longest duration of sustained cocaine abstinence (P=.001), increased the percent of subjects who were cocaine abstinent (P<.001) and opiate abstinent (P=.031) across the 12 weeks of the voucher intervention, and significantly decreased reports of cocaine craving (P=.046). Unexpectedly, adding start-up bonuses significantly decreased the percent of subjects who were cocaine abstinent, relative to abstinence rates under the escalating pay schedule alone (P≤.05). These results replicate the efficacy of voucher-based reinforcement of cocaine abstinence, show that it can have broad beneficial effects as evidenced by its effects on opiate use, and demonstrate that the schedule of reinforcement can be an important determinant of efficacy. Further exploration of basic parameters of operant conditioning may help identify the most effective methods of motivating cocaine abstinence in chronic drug abusers.

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EARLY ABSTINENCE PREDICTS OUTCOME IN BEHAVIORAL TREATMENT FOR COCAINE DEPENDENCE

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Behavioral treatment that integrates a voucher program and the Community Reinforcement Approach (CRA) is effective in facilitating cocaine abstinence. This study attempted to better understand the effects achieved with this intervention. 86 cocaine-dependent clients received the 24-week treatment. Cocaine use during three periods (Wkl, Wk2, Wk3) was examined as a predictor of six month outcome. Abstinence status during Week 2 was a more accurate predictor than Week 1, and was not different than Week 3. The Week 2-abstinent group completed 21 weeks of treatment on average compared lo 16 weeks for the Week 2-positive group ($p<.01$). Among the Week 2-abstinent group, 06%, 65% and 52% achieved > 3, 8 and 12 weeks, respectively, of continuous cocaine abstinence compared to 41%, 10% and 16% in the Week 2-positive group ($p<.01$). Logistic regression indicated that frequency of cocaine and marijuana use and alcohol dependence were significant predictors of Week 2 abstinence status. Multiple regression indicated that Week 2 abstinence status predicted outcome ($R2=.21$) better than any pretreatment variables. Week 2 abstinence status was also associated with six month outcome in clients who received two different treatments for cocaine dependence (CRA-only and standard drug counseling). Comparisons across treatments showed that, among both Week 2-positive and Week 2-abstinent, CRA with vouchers produced greater periods of cocaine abstinence. These findings indicate that cocaine abstinence achieved early in treatment is a robust predictor of six month outcome. Clients who do not achieve early abstinence are less likely to achieve significant periods of abstinence. Specific treatments can enhance outcome in clients who do not achieve early abstinence. Examination of clinical strategies targeting early abstinence and alternative strategies for those who do not achieve early abstinence appears warranted.

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RELAPSE PREVENTION TREATMENT FOR COCAINE DEPENDENCE: GROUP VERSUS INDIVIDUAL FORMAT

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The present study sought to assess the effectiveness of GROUP vs. INDIVIDUALLY-BASED Relapse Prevention therapy in a sample of recently hospitalized cocaine dependent patients who were seeking additional treatment on an outpatient basis. Thirty-two cocaine dependent patients were randomly assigned by cohorts to Group-based RP (G-RP) or Individually-based RP (I-RP). The two RP formats were identical in content, consisting of 12 treatment sessions over a two month period immediately following hospitalization. We obtained complete self-report and urine drug screen data at pretreatment, posttreatment and three month and six month follow-up for the 32 subjects (16 per condition); treatment outcome was evaluated in terms of both psychosocial and drug-use variables. No pretreatment differences were noted across treatment conditions in age, education, employment status, cocaine use history, or addiction severity indices. There was a non-significant trend suggesting less cocaine use during treatment in patients receiving group therapy compared to those receiving individual therapy. At follow-up assessments no differences in cocaine use as a function of treatment format were found. Other outcome measures suggest overall treatment- related improvement in psychosocial functioning and coping. Patients receiving group therapy show a greater reduction in psychiatric symptomatology at posttreatment. At three months, % of subjects were cocaine-free, whereas % were cocaine-free at six months. Patients diagnosed as cocaine and alcohol dependent were more likely to be using cocaine during treatment and follow-up compared to cocaine dependent patients who were not alcohol dependent. These outcome results suggest that RP therapy format does not produce differential short-term treatment effects on cocaine use.

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PATIENT-TREATMENT MATCHING EFFECTS IN AN OUTPATIENT TRIAL OF GROUP PSYCHOTHERAPY FOR COCAINE ABUSE: PRELIMINARY ANALYSES

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This study is evaluating the efficacy of a cognitive-behavioral group and a 12-step facilitation group in treating cocaine abuse. Subjects (n=140) are randomly assigned to treatment conditions, and assessed at baseline and weeks 4, 8, 12, and 26. Both treatment conditions offer 36 group therapy sessions over a 12 week period. We hypothesized that: (a) 12-step facilitation would be differentially effective for patients who evidenced high levels of religious behaviors, and who endorsed a disease model of addictive behavior; and (b) cognitive-behavioral treatment would be differentially effective for subjects who had higher abstract reasoning skills, who had greater drug use severity, and who had a history of Major Depression. Analyses conducted on the first 60 subjects to complete 12 weeks of the study revealed that, among 12-step treatment subjects, those with high levels of endorsement of a disease model were more likely to achieve three weeks of continuous abstinence than subjects with low levels of endorsement. Similarly, 12-step subjects who reported high levels of religious behavior at intake were significantly more likely to achieve three weeks of continuous abstinence than subjects with low levels of religious behavior. In the cognitive-behavioral condition, subjects who demonstrated higher abstract reasoning or who had histories of depression had better outcomes, but the effects only approached significance in this partial sample.

CONFORMATIONAL ANALYSIS OF ANANDAMIDE ANALOGS AND ITS RELATIONSHIP TO A CANNABINOID PHARMACOPHORE

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Molecular dynamics have been performed on a series of fatty acid ethanolamides that are structural analogs of anandamide (AN), an endogenously occurring cannabimimetic. We have characterized the conformational mobility of these compounds and found that a looped-conformation of arachidonyl compounds is energetically favorable wherein a structural correlation between anandamides and classical cannabinoids can be obtained with the superposition of 1) the oxygen atom of the carboxy-amide in AN with the pyran oxygen in Δ^9-THC, 2) the ethanolic hydroxyl of AN with the phenolic hydroxyl in Δ^9-THC, 3) the alkyl "side chain" of AN aligned with the side chain of Δ^9-THC, and4) the polyolefin loop overlaying the ring system in Δ^9-THC. This shape similarity is extended to show that the ability to overlay with Δ^9-THC is dependent upon the number of double bonds in the fatty acid's structure, with an optimal distance and molecular volume overlap occurring at the tetraene analog (*i.e.,* anandamide itself). The ability to incorporate the structure and potency of anandamide analogs into a three-dimensional quantitative structure-activity model of the cannabinoid pharmacophore that includes classical and nonclassical cannabinoids supports the relevance and coherence of the proposed alignment and model.

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AN AUTORADIOGRAPHIC COMPARISON OF CP-55,940 AND ANANDAMIDE RECEPTOR BINDING IN THE RAT BRAIN

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Recent evidence implicates anandamide as the endogenous ligand for the cannabinoid receptor. Although anandamide exhibits cannabimimetic properties, anandamide did differ pharmacologically from Δ^{9}-THC in respect to duration of action, potency and antinociception. This study' was undertaken to compare binding localization between anandamide and CP-55,940 in slide-mounted serial sections of rat brain using [^{3}H]-CP-55,940. Three areas of the brain were selected for comparison: Caudate-putamen, hippocampus and cerebellum. Slices treated with [^{3}H]-CP-55,940 were incubated for two hours with either CP-55,940 or anandamide followed by a four hour wash. A K_d of 15.3 nM and a B_{max} of 72.8 pM (n=5) for the caudate-putamen were obtained by liquid scintillation. Anandamide produced a K_i of 8032 ± 1110 nM (n=3). Inclusion of the enzyme inhibitor PMSF in incubation yielded a K_i 320 ± 529 nM (n=6), and a 30 minute pretreatment with PMSF lowered the K_i to 608 ± 209 (n=3). PMSF was therefore included in pretreatment and incubation for anandamide. In autoradiography assays, slices were apposed to film for three weeks. K_i values were determined for CP-55,940 by autoradiography in the lateral caudate putamen (14.7 nM), CA3 region of the hippocampus (11.8 nM) and the molecular of the cerebellum (15.3 nM). K_is for anandamide were 575 nM (caudate-putamen) and 993 nM (CA3). These assay conditions allow binding of anandamide and CP-55,940 to be compared in discret anatomic al locations.

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SPECIFICITY OF THE ANTAGONIST SR141716A IN THE MOUSE MODEL OF CANNABINOID ACTIVITY AND IDENTIFICATION OF AGONIST ACTIVITY

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SR141716A can antagonize the *in vivo* effects of the nonclassical cannabinoid WIN 55,212 (Rinaldi-Carmona *et al.,* 1994). Additionally, it was found to be without agonist activity, and specificity was demonstrated by the lack of antagonism of the hypothermic effect of reserpine, oxotremorine or apomorphine. However, *in vivo* antagonism was not demonstrated against the prototypical cannabinoid Δ^{9}-tetrahydrocannabinol Δ^{9}-THC). Pretreatment with SR141716A (i.v.) resulted in antagonism of the effects of Δ^{9}-THC (1 mg/kg, i.v.) on mouse spontaneous activity, temperature and tail-flick response with AD_{50} values (mg/kg; 95% c.1.) of 0.12 (0.02-0.66), 0.43 (0.14-1.3) and 13.2 (5.6-31), respectively. The large (30-100 times) difference in antagonist potency for blocking the antinociceptive effect versus the other measure was unexpected, though a small difference in potency (six times) between the hypothermic and antinociceptive measures had been reported previously. Subsequently, it was observed that the antinociceptive effect (%MPE) of morphine (4 mg/kg, i.p.) in the tail-flick procedure was reduced from 7.5% (±8) to 40% (±9) by the largest dose of SR141716A evaluated (30 mg/kg). Therefore, complete dose-response analysis of morphine in the presence and absence of SR141716A was performed. A dose of 30 mg/kg antagonist produced a significant ($p < 0.05$) rightward shift in the morphine-%MPE curve, with a resulting ED_{50} value (±S.E.) of 5.3 (± 0.6) mg/kg, compared to a control value of 3.2 (± 0.3). During the evaluation of SR141716A (3-30 mg/kg, i.v.) for potential agonist activity, it was observed that the drug increased locomotor activity (counts/10 min) from 1456 (±188) to 4068 (±178), and did so in a dose-responsive fashion exhibiting an ED_{200} of 7.9 mg/kg.

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COMPARISON OF Δ^9-THC AND ANANDAMIDE TOLERANCE

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The cannabinoid Δ^9-THC and potent bicyclic analog CP-55,940 have been found to produce different degrees of pharmacological tolerance in mice. In previous studies, chronic CP-55,940 produced a 100-fold increase in ED_{50} values compared to a 10-fold increase produced by Δ^9-THC. Whether a more rigorous Δ^9-THC drug dosing regimen would produce tolerance comparable to that of CP-55,940 is unknown. Therefore, the first objective was to determine if a greater magnituude of tolerance to Δ^9-THC could be achieved using a more stringent dosing regimen. The endogenous cannabinoid ligand anandamide is pharmacologically similar to Δ^9-THC and CP-55,940, but it is unknown whelher anandamide would have a similar profile for tolerance development. Therefore, the second objective is 10 determine whether tolerance occurs to anandamide after a rigorous chronic treatment regimen. Previously, tolerance to Δ^9-THC has been achieved by administrating 10 mg/kg s.c. for seven days, two times a week. In this study four drug dosing regimens of fixed or incrementing doses two times daily, s.c. or i.p., for either one or two weeks were tested. Six drug dosing regimens for anandamide, s.c. or i.p. injections four times daily (due to its apparent short half-life) for one or two weeks, were evaluated. The highest non-toxic dosing regimen was used to evaluate pharmacological tolerance. For Δ^9-THC, mice were dosed one week, s.c, two times daily with vehicle or Δ^9-THC (50 to 200 mg/kg). For anandamide, mice were injected s.c. for three days, four times a day, with 100 mg/kg anandamide. After completing the drug regimen, the mice were tested for hypoactivity and antinociception following i.v. administration of vehicle or test drug. For vehicle- and Δ^9-THC-treated mice the ED_{50} values were 1 and 10 mg/kg for hypoactivity and 0.5 and 35 mg/kg for antinociception, respectively. The ED_{50} values for vehicle- and anandamide-treated mice were 22.5 and 13.5 mg/kg for hypoactivity and 8.8 and 4.0 mg/kg for antinociception, respectively. Substantial pharmacological tolerance developed to Δ^9-THC though this was of a lesser magnitude than CP-55,940; no tolerance developed to anandamide.

THE CANNABINOID RECEPTOR ANTAGONIST SR141716A BLOCKS ANANDAMIDE-AND Δ^9-THC-INDUCED ARACHIDONIC ACID RELEASE IN ASTROGLIAL CELLS

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The psychoactive cannabinoids slimulate arachidonic acid release which results in the generation of biologically active eicosanoids. The purpose of this study was to examine whether the cannabinoid receptor antagonist, SR141716A, blocks anandamide- or Δ^9-THC-evoked arachidonic acid release in rat cortical astrocytes and, if so, whether cortical astrocytes contain the cannahinoid receptor. The cortical astrocytes from one day old rat brain were grown to confluency in serum supplemented Dulbecco's Modified Eagle's Medium (DMEM). The [^{3}H]arachidonic acid labeled cell monolayer was preincubated for 10 minutes at 37°C in DMEM with or without the acyltransferase inhibitor-thimerosal, amidase inhibitor-PMSF, and SR141716A. Cells were then incubated for 20 minutes with fresh medium with or without anandamide or Δ^9-THC. Aliquots of the medium were counted for released radioactivity. Our results show that both anandamide and Δ^9-THC stimulated arachidonic acid release by more than 2-fold over the thimerosal control. The release of arachidonic acid was blocked by SR141716A. A 10 μM concentration of SRl41716A was needed to block >90% of the anandamide-induced arachidonic acid release. In contrast, lower concentrations of SR141716A caused statistically significant blockade of Δ^9-THC-induced arachidonic acid release indicating the cannabinoid receptor involvement. To determine the mRNA for the cannabinoid receptor, total RNA was extracted from astrocytes, polyA+ mRNA separated, and further resolved by electrophoresis. The mRNA was transferred by diffusion blotting to nylon membrane and then hybridized to [^{32}P] labeled cDNA probes for the cannabinoid receptor subtypes. Our results show that astrocytes contain the mRNA for CB1 subtype but not CB2. Our results suggest that anandamide and Δ^9-THC-induced arachidonic acid release from astrocytes may be cannabinoid receptor-mediated.

ANTAGONISM OF THE CANNABIMIMETIC EFFECTS OF Δ^9-THC

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SR141716A, a recently developed cannabinoid antagonist, binds to brain cannabinoid receptors and blocks characteristic pharmacological effects of naturally occurring and synthetic cannabinoids, including Δ^9-tetrahydrocannabinol (Δ^9-THC), anandamide, and WIN 55,212-2. The present study investigated the effects of this compound in an animal model of cannabis intoxication. Rats were trained to discriminate 3 mg/kg Δ^9-THC from vehicle in a two-lever drug discrimination procedure. Rhesus monkeys were also trained to discriminate between Δ^9-THC and vehicle. Results of tests with various doses of SR141716A in combination with 3 mg/kg Δ^9-THC showed that SR141716A produced dose-dependent antagonism of the discriminative stimulus properties of Δ^9-THC in rats, with recovery within 24 hours. SR141716A also blocked the discriminative stimulus effects of Δ^9-THC in monkeys. Further, 1 mg/kg SR141716A produced rightward shifts in the Δ^9-THC and WIN 55,212-2 dose-effect curves in rats. When administered alone, SR141716A did not substitute for Δ^9-THC. The present results suggest that SR141716A blocks the discriminative stimulus effects of Δ^9-THC via a receptor-mediated mechanism.

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(R)-METHANANDAMIDE, BUT NOT ANANDAMIDE GENERALIZES TO THE DISCRIMINATIVE STIMULUS PROPERTIES OF Δ^9-THC

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Fifteen male rats were trained to discriminate between injections of 2 mg/kg Δ^9-THC and vehicle (20 min post-injection) in a 2-lever operant drug-discrimination paradigm. After training, Experiment 1 revealed that anandamide (0.5-16 mg/kg/i.p.), the putative endogenous cannabinoid receptor ligand, failed to generalize to the discriminative stimulus properties of the training dose of Δ^9-THC. Since anandamide has previously been shown to have a shorter duration of action than Δ^9-THC, Experiment 2 reevaluated the discriminative stimulus properties of anandamide five minutes following injection. Consistent with the first experiment, results of Experiment 2 showed that anandamide failed to generalize to the discriminative stimulus properties of Δ^9-THC. A third experiment found that (R)-methanandamide (0.5-8 mg/kg/i.p.), a metabolically stable analog of anandamide, did generalize to the discriminative stimulus effects of Δ^9-THC. Collectively, these results suggest that the naturally occuring form of anandamide does not produce a cannabimimetic interoceptive state, however, this failure is most likely due to the rapid metabolic conversion of systemically administered anandamide.

MIDDLE LATENCY EVOKED POTENTIALS (ERPs) IN MEDICALLY AND PSYCHIATRICALLY NORMAL THC USERS

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Because pilot findings (G. Racagni *et. al.* (eds.) Biological Psychiatry, Vol. 2, Elsevier Science Publications, New York, 1991, pp.21-24) suggesting that brain stem, cognitive P300 and some middle latency ERPs might be altered in THC users were flawed by uncontrolled psychiatric diagnostic and medication variables, a study of rigorously screened medically and psychiatrically normal THC users and controls was undertaken. Using normal Ss with controls for age, THC users and controls did not differ on auditory brainstem and auditory and visual P300 responses (Clin. Electroenceph., 25:1-7, 1994; Life., 56: 2135-2140, 1995). This report analyzes the latencies and amplitudes of the left and right visual P100; left somatosensory N18, P30, N60; and auditory P50, N90, P150, N250 in 36 normal daily THC users and 45 normal controls. Initial analyses suggested that THC users had reduced right visual P100 amplitudes ($p=.046$), increased left somatosensory N18 amplitudes ($p=.025$), and (c) increased auditory P50 amplitudes ($p=.019$). However, when between group age differences ($p=.009$) are removed, only the elevated auditory P50 amplitude for THC users remains significant. No ERP differences between THC users with $\geq$15 years of daily THC use and age matched controls were found. We conclude that, among normals, ERP sequelae of chronic THC use are not impressive.

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INHIBITION OF CYP2D DOES NOT ALTER THE BEHAVIORAL EFFECTS OF HYDROCODONE IN RHESUS MONKEYS

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The role of cytochrome P450 in the effects of opioids was examined in monkeys by comparing the discriminative stimulus and antinociceptive effects of hydrocodone (HC) and hydromorphone (HM) alone and in The presence of inhibitors of a P450 isozyme (CYMD). HC and HM had morphine-like discriminative stimulus effects and both compounds were fully-effective in a warm-water tail withdrawal procedure of antinociception. Neither budipine nor quinidine, both of which inhibit CYP2D *in vitro,* reliably altered the potency or the duration of action of HC; naltrexone dose-dependently antagonized the discriminative stimulus and antinociceptive effects of HC and HM. Blood specimens obtained during antinociception studies showed an inhibition by budipine of the conversion of HC to HM. For example, the ratio of plasma HC/HM in monkeys receiving 3.2 mg/kg of HC was 2.3 (1.4-3.3); in monkeys receiving 10.0 mg/kg budipine and 3.2 mg/kg of HC the ratio was 5.8 (3.0-9.3). These data suggest that is not critical to the expression of behavioral effects for HC, perhaps because HC itself might have agonist actions under these conditions that are indistinguishable from the agonist effects of HM.

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DISCRIMINATIVE STIMULUS PROPERTIES, MOTOR AND MEMORY EFFECTS OF DEXTROMETHORPHAN AND DEXTRORPHAN IN RATS

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The phencyclidine (PCP)-like antagonists of the N-Methyl-D-Aspartate (NMDA)-receptors possess anticonvulsant and neuroprotective properties but they lead to abuse, psychotomimetic symptoms, motor effects and memory impairment. Dextromethorphan (DM) and its metabolite dextrorphan (DX), two synthetic antitussives and PCP-like antagonists, would be better tolerated. Sprague-Dawley rats were trained to discriminate between intraperitoneal administration of DM (30 mg/kg) and saline using a standard two-lever, fixed ratio 10, food reinforcement procedure. DX, dizocilpine and cyclazocine induced a complete generalization to DM, but with a dose higher than the DM training dose for DX, and with a dose that reduced the number of rats responding for dizocilpine. Morphine, U 50488, carbetapentane and caramiphen did not substitute for DM. Wistar rats were used to assess motor effects in an open-field and in a circular pool, and memory impairment in the Morris water maze. DX induced dose-dependent stereotypy (20 mg/kg), ataxia (30 mg/kg) and an increased locomotion (40 mg/kg). DM induced fewer locomotion (30 mg/kg) and stereotypy (40 mg/kg), and a moderate ataxia (40 mg/kg). DM (10,20,30 mg/kg) and DX (5 mg/kg) did not disrupt the spatial learning. DX (10, 15 mg/kg) partially blocked spatial learning, during seven days after the highest dose. The retention of the spatial learning acquired without treatment was not impaired by DM (10, 20, 30 mg/kg) or DX (5, 10, 15 mg/kg). DM (30 mg/kg) moderately impaired the working memory while DX (5, 10, 15 mg/kg) did not. Reference memory was not disturbed by DM (10 to 30 mg/kg) or DX (5 to 15 mg/kg). The discriminative stimulus of DM did not result primarily from its metabolism to DX. The similarity of the DM and cyclazocine discriminative stimulus properties suggests an involvement of sigma- and PCP-sites in the mediation of the DM stimulus. DX induced PCP-like motor and memory effects. DM induced sedative effects. This may be related to the higher affinity of DX for the PCP-sites while DM has a higher affinity to both the DM- and sigma-receptors. Considering me few and minor side effects, particularly with DM, these two drugs may have therapeutic interest.

DISCRIMINATIVE STIMULUS PROPERTIES OF MORPHINE IN FEMALE AND MALE RATS

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Gender differences in rates of drug addiction may reflect biological differences in sensitivity to the subjective or reinforcing properties of abused substances. The present study was conducted to determine whether female and male rats show any differences in rate of acquisition of a morphine discrimination, and whether there are sex differences in sensitivity to the discriminative effects of μ, κ, and δ opioid agonists. Female and male Sprague-Dawley rats were trained to discriminate 3.0 mg/kg s.c. morphine from saline in a two-lever, food-reinforced operant procedure. Female rats acquired the morphine discrimination faster than male rats did (mean 29.2 vs. 51.3 sessions, respectively). Moreover, the ED50 for morphine was slightly lower in female rats than in male rats (0.66 vs. 1.29 mg/kg, respectively), although the time course of morphine discrimination was similar between the two sexes. The μ agonist fentanyl (0.003-0.03 mg/kg) fully substituted for morphine in both female and male rats, with no potency differences. In contrast, the κ agonist U69,593 (0.1-0.3 mg/kg) did not substitute for morphine in either sex, and the δ agonist BW373U86 (0.1-10.0 mg/kg) partially substituted for morphine in both sexes. The partial μ agonist buprenorphine (0.003-0.1 mg/kg) has thus far substituted fully in two of two females tested, and in three of five males tested. Although female rats were more sensitive than male rats to morphine's discriminative stimulus effects, they were less sensitive than males to morphine's antinociceptive effects, which suggests that sex differences in behavioral effects of morphine are probably not simply due to sex differences in pharmacokinetics.

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MULTI-ELEMENTAL DISCRIMINATIVE STIMULUS CONTROL: EFFECTS OF SACCHARIN CONCENTRATION

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The effects of the saccharin concentration used on the stimulus control exerted by a multi-elemental stimulus consisting of morphine (5.6 mg/kg), saccharin (0.01, 0.03, or 0.10 %, w/v), and a ball-bearing drinking nozzle in a discriminated taste aversion procedure was examined. In this discriminated taste (DTA) aversion procedure, male Taconic Sprague-Dawley rats received injections of lithium chloride (LiCl) following presentation of this multi-elemental stimulus, and injections of saline (10 ml/kg) following the saline (1 ml/kg), water, and non-ball bearing nozzle composite stimulus. These paired rats (n=12 per group) were compared 10 unpaired rats (n=6 per group) that received saline injections rather than LiCl injections following presentation of the drug/taste/tactile stimulus composite. Morphine and saline (1 ml/kg) were injected 20 minutes before drinking. Analysis of variance suggested that the formation of DTA was a function of the saccharin concentration offered for drinking and most rapid for the highest concentration. In subsequent testing with each individual stimulus element and combinations of two stimulus elements, stimulus control was clearly exerted by all the three stimulus elements (saccharin/nozzle/morphine). When another stimulus element was presented jointly with saccharin, behaviorat conlrot was similar to that of saccharin atone. Behavioral control by saccharin increased with saccharin concentration. However, behavioral control by the two other stimulus elements was relatively unaffected by increasing the saliency of the saccharin element.

EFFECT OF FOOD DEPRIVATION AND SATIATION ON SENSITIVITY TO THE DISCRIMINATIVE-STIMULUS EFFECTS OF PENTOBARBITAL IN PIGEONS AND MORPHINE IN RATS

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Food deprivation can produce substantial increases in the self-administration of drugs of abuse, suggesting that food deprivation increases their reinforcing-stimulus properties. This finding has been replicated with a wide variety of drugs under a wide variety of conditions. The present experiments examined the effects of food deprivation and saliation on the discriminative-stimulus properties of drugs to determine if food deprivation affects the discriminative-slimulus effecls of drugs in a manner similar to its effects on the reinforcing-stimulus properties. Rats were trained lo discriminate 10 mg/kg, i.p., morphine from saline and dose-effect curves for morphine were then determined when the animals were either food-deprived (85% free feeding body weight) or after a 15-minute supplemental feeding just prior to testing. The ED_{50} value for the food-deprived condition was not significantly different from the ED_{50} value for the food-saliated condition (3.6 vs. 4.8 mg/kg, respectively). In another experiment, pigeons were trained lo discriminate 5 mg/kg, i.m., pentobarbital from saline. Dose-effect curves were determined under food-deprivation conditions (80% free-feeding body weight) and under partial food-satiation conditions (25% and 50% of the amount of full satiation). It was found that generalization curves for both pentobarbital and saline were similar at all levels of food deprivation. Thus, in both pigeons and rats, there was little evidence that food deprivation increased the sensitivity to the discriminative-slimulus properties of drugs in the same way the food deprivation increases the reinforcing-stimulus properties of drugs. In conclusion, food deprivation must increase drug self-administration by a mechanism other than by increasing the discriminative-stimulus properties of drugs.

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EFFECTS OF CTAP IN MORPHINE-DEPENDENT PIGEONS DISCRIMINATING MORPHINE, SALINE, AND NALTREXONE

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Cyclic somatostatin analog D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Pen-Thr-NH_2 (CTAP) is a putative μ opioid receptor neutral antagonist. Experiments examined whether cumulative doses of CTAP (0.1-100 ug, icv), would alter discriminative stimulus effects of morphine (MS) or naltrexone (NTX) in five MS-dependent pigeons (10 mg/kg/day MS) trained to discriminate 17.8 mg/kg MS, 0.056 mg/kg NTX and saline (SAL) under FR 30 schedules of food reinforcement. When given atone, CTAP produced neither MS-like nor NTX-like stimulus effects. CTAP failed to reverse the stimulus effects of 17.8 mg/kg MS. When given 0.056 mg/kg NTX, CTAP reversed the NTX cue, without producing MS-like stimulus effects. In contrast, CTAP did not reverse the NTX-like stimulus effects of 30-h withdrawal from MS. Overall, these effects do not mimic those of high efficacy μ agonists (which produce MS-like effects and reverse NTX-like effects), antagonists (which produce NTX-like effects and reverse MS-like effects), or partial agonists (which do not produce MS-like effects, but rather reverse NTX-like effects of NTX or 30-h withdrawal) in morphine-treated pigeons. These data suggest CTAP has an unique profile of action unlike agonists, antagonists, or partial agonists.

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INTERACTIONS BETWEEN THE DISCRIMINATIVE STIMULUS EFFECTS OF MU OPIOIDS AND THE DELTA OPIOID BW373U86

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The delta opioid agonist BW373U86 was examined atone and in combination with mu agonists in two groups of subjects: (1) pigeons trained to discriminate the mu agonist fentanyl (0.056 mg/kg), the kappa agonist bremazocine (0.017 mg/kg) and saline in a three-choice discrimination, and (2) rats trained to discriminate the mu agonist morphine (3.0 mg/kg) from saline in a two-choice discrimination. In the pigeons, BW373U86 (0.01-10.0 mg/kg) produced a dose-dependent increase in fentanyl-appropriate responding and complete generalization to fentanyt in four of five subjects. Fentanyl-appropriate responding elicited by 10.0 mg/kg BW373U86 may have been mediated by delta opioid receptors, because this effect was antagonized by the delta selective antagonist naltrindole (0.1-10.0 mg/kg) but not by the mu selective antagonist naloxone (0.1-30.0 mg/kg). In the rats, BW373U86 (0.3-10.0 mg/kg) elicited primarily saline-appropriate responding. Subsequently, BW373U86 was administered in combination with fentanyl, morphine and nalbuphine in the pigeons and in combination with fentanyl and morphine in the rats. In the pigeons, a low dose of BW373U86 (0.01 mg/kg) that elicited primarily saline-appropriate responding when administered alone did not produce a significant change in the ED50 values for fentanyl, morphine or nalbuphine. Combinations of these mu agonists with higher doses of BW373U86 (0.1-1.0 mg/kg) produced generally additive effects. In the rats, BW373U86 (0.3-3.0 mg/kg) had no effect on the fentanyl or morphine dose-effect curves. These results indicate that BW373U86 shares discriminative stimulus properties with mu agonists in the pigeon but not in the rat. In addition, BW373U86 does not alter the discriminative stimulus effects of mu agonists in either rats or pigeons.

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EFFECTS OF THE IRREVERSIBLE ANTAGONIST B-FNA ON THE DISCRIMINATIVE STIMULUS EFFECTS OF MU OPIOIDS

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Pigeons (n=7) were trained to discriminate 3.0 mg/kg morphine from water in a cumulative dosing drug discrimination procedure. The mu opioids fentanyl, morphine and nalbuphine substituted completely for the training stimulus. The pigeons were then pretreated with a 10.0 mg/kg dose of the irreversible competitive antagonist B-FNA. When nalbuphine was tested two hours after pretreatment with B-FNA, there was a 1.26 log unit rightward shift in the dose-effect curve. When tested two and six days later, the dose-effect curve had returned to control values. When the morphine dose-effect curve was redetermined two hours after B-FNA administration, there was a 0.42 log unit shift in the dose-effect curve. The dose-effect curve for morphine had returned to control values when tested two and six days after B-FNA pretreatment. When tested two hours, two days, and six days after administration of B-FNA, the dose-effect curve for fentanyl was not altered. The differential degree of shifts in the dose-effect curves correlate with the different relative intrinsic efficacies of these drugs (fentanyl > morphine > nalbuphine) and arc consistent with data obtained with these opioids when tested in antinociceptive assays. Further tests have demonstrated that the antagonism is dose-dependent, in that a lower dose of B-FNA shifts the nalbuphine dose-effect curve to a smaller degree. A time course analysis showed that the dose-effect curve returns to control levels by 26 hours after B-FNA pretreatment and that there is no subsequent leftward shift in the dose-effect curve.

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BEHAVIORAL EFFECTS OF DYNORPHIN A(1-13) IN UNTREATED AND IN MORPHINE-TREATED RHESUS MONKEYS

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The current studies evaluated the effects of dynorphin A(1-13) [DYN] in rhesus monkeys. In monkeys discriminating between EKC and saline, DYN did not substitute for the EKC discriminative stimulus. In morphine-treated (3.2 mg/kg/day) monkeys discriminating between NTX and saline, DYN did not substitute for, or modify, the discriminative stimulus effects of NTX or morphine. Rate-decreasing effects of DYN were greatest one to six minutes after injection and were not attenuated by a dose of 1.0 mg/kg of quadoazocine. The antinociceptive effects of morphine were not modified by DYN; however, monkeys tolerant to antinociceptive effects of morphine also appeared to be tolerant to the antinociceptive effects of DYN but not to enadoline or U-50,488. DYN produced salivation, eye closure, mydriasis and flushing and these effects were not attenuated by chlorpheniramine, PCP or quadazocine. That cross tolerance did not develop between morphine and enadoline or U-50,488, provides further evidence of differences between DYN and other κ agonists. Moreover, the lack of antagonism of DYN by quadazocine and the lack of substitution by DYN for either μ or κ opioids support the notion that DYN has significant non-opioid effects.

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THE DISCRIMINATIVE STIMULUS EFFECTS OF THE SELECTIVE KAPPA OPIOID CI 977 IN SQUIRREL MONKEYS

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Kappa opioid agonists have behavioral effects in primates that differ from those of other opioids and that are thought to be mediated via kappa receptor activation. The present studies were conducted to characterize the effects of kappa opioids in squirrel monkeys trained to discriminate injections of the selective kappa agonist CI 977 (1.7µg/kg) from injections of saline. After training was completed (65-134 sessions) the effects of CI 977 (Cl; 0.3-3.0µg/kg), kappa opioids including PD117302 (PD; 30-300µg/kg). U50488H (U50; 30-300µg/kg), bremazocine (BMC; 0.3-3.0µg/kg), ethylketocyclazocine (EKC; 3.0-30µg/kg), GR89686A (GR; 0.3-3.0µg/kg), (-)spiradoline [(-)SP; 10-100µg/kg], the inactive enantiomer (+)spiradoline ((+)SP; 0.001-3.0mg/kg), the µ opioid morphine (MORP; 0.3-1.0mg/kg), the ∂ opioid Bw373 (BW; 0.01-1.0mg/kg), butorphanol (BUT; 0.03-1.0mg/kg) and nalbuphine (NLB; 0.1-3.0mg/kg) were determined in all monkeys. In addition the effects of pretreatment with the opioid antagonist quadazocine were determined. Results show that CI, PD, U50, BMC, EKC, GR and (-)SP, but not (+) SPR, MORP, BW, BUT and NLB fully substituted for CI 977 in all animals. Analysis of the quadazocine antagonism revealed an apparent pA_2 of 6.9±0.4. These results suggests that the effects of CI977 are mediated by its actions at kappa receptors.

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ASSESSMENT OF µ-OPIOID RECEPTOR TURNOVER USING ß-FNA IN RATS

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Previous reports from our laboratory indicate that the time course of ß-FNA's effects on heroin self-administration and µ-opioid receptor binding are not correlated (Martin *et. al.,* 1995). This study was initiated to estimate the half-life of µ-opioid receptors using *in vivo* antagonism of heroin self-administration as the pharmacological measure. The dose-response curve for heroin self-administration was determined before and each day after i.c.v. administration of 40 nmol of ß-FNA for 30 days. The fraction of remaining receptors was calculated from the inverse of the slope of a plot of equiactive doses of heroin before and successive days after ß-FNA. ß-FNA shifted the dose-effect curve slightly downward and 30-fold to the right. ß-FNA significantly increased the ED_{50} for heroin from 3.5 (2.4, 4.8) [mean (95% C.L.)] to 29.4 (10.5, 70.2) µg/inf on the ascending limb and from 16.2 (12.5, 19.9) to 510.5 (326.6, 783.4) µg/inf on the descending limb of the dose-response curve. The slope of the ascending limb of the dose-response curve was significantly decreased from 10.8 (8.1, 12.0) to 4.7 (3.3, 6.6) inf/log/µg/inf) following ß-FNA, but the slope of the descending limb was unaffected (-12.2 (-10.5, -15.2) for control vs. -9.5 (-8.4, -11.3)) following ß-FNA. Calculation of the q-value for the equiactive doses revealed that ß-FNA administration resulted in a 94.4% depletion of the receptor population that heroin interacts with to maintain responding. There was an initial lag in the return of heroin self-administration, followed by a return that was consistent with mono-exponential kinetics 21 days after ß-FNA. The half-life of µ-opioid receptors was 1.4 days from days 21-30. These data suggest that ß-FNA continues to alkylate µ-opioid receptors for some time after i.c.v. administration of 40 nmol and that the µ-opioid receptor turnover is 1.4 days when the depot of ß-FNA is sufficiently depleted to allow receptor repopulation.

HEROIN SMOKING IN RHESUS MONKEYS

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There is an increasing trend of heroin smoking in the U.S. The current study was undertaken to extend this laboratory's previously established cocaine smoking procedure to heroin self-administration. Rhesus monkeys (N=8; 85% free-feeding weight) were trained under a chained schedule requiring a fixed ratio (FR) lever press and inhalation sequence. The dose of heroin available for self-administration was 0.1 mg/kg/delivery and the maximum daily deliveries available was ten during the daily four hour sessions. Demand for heroin was assessed by measuring smoke deliveries as a function of price (FR 16-1024), it was compared to the demand for cocaine base. Dose-effect functions were obtained across a range of doses (0.025-1.6 mg/kg/delivery). Substitution tests were obtained using the peripheral-acting opioid agonist, loperamide (0.05 mg/kg/delivery). Lastly, tests with naloxone (0.01-1.0 mg/kg i.m., 10 min pre-session) were conducted. All monkeys readily acquired heroin self-administration. Increases in the FR requirement resulted in decreases in the number of inhalations self-administered, with an - 80% reduction at the highest FR tested. The heroin demand function was shifted to the left of the cocaine base demand curve, suggesting that heroin was less reinforcing than cocaine. Increases in the unit dose of heroin resulted in a shallow inverted "U"-shaped function. Substituting loperamide for heroin resulted in a greater than 80% reduction in the number of deliveries in 8-15 days and responding returned to baseline levels with heroin reinstatement. Naloxone produced dose-dependent decreases in the number of heroin inhalations with the 1.0 mg/kg dose producing complete suppression of heroin self-administration. These data suggest that rhesus monkeys readily self-administer smoked heroin and behavioral and pharmacological manipulations alter the rate of self-administration.

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SENSITIZATION TO THE CONDITIONED REWARDING EFFECTS OF MORPHINE: ROLE OF δ-OPIOID RECEPTORS AND DOPAMINE

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The issue of whether sensitization develops to the conditioned rewarding effects of morphine was assessed by use of an unbiased place preference conditioning procedure. Male Sprague-Dawley rats received once daily injections of saline, morphine (5.0 mg/kg), fentanyl (0.016 mg/kg) or nicotine (0.6 mg/kg) for five days in a room distinct from that where conditioning occurred. Place conditioning sessions commenced three days later and were conducted on days eight through ten. Tests of conditioning were conducted one day later. A minimum of six conditioning sessions was necessary for the establishment of morphine-induced place preferences in control animals. The minimum effective dose was 5.0 mg/kg. In animals previously exposed 10 morphine, fentanyl or nicotine, conditioned place preferences were observed after only four sessions and in response to doses of 3.0 mg/kg and greater. An enhanced response to morphine was apparent when conditioning commenced 3, 14 or 21 days after the cessation of opiate preexposure. It was not apparent on day one. In animals which received the five day opiate treatment in combination with the δ-opioid receptor antagonist naltrindole (0.03-1.0 mg/kg) or a high dose (0.5 mg/kg) of naloxone, the enhanced response to morphine was prevented. Thus, in these animals, morphine in doses of 1.0-5.0 mg/kg was ineffective as a conditioning stimulus. Neither antagonist modified the nicotine-induced enhancement of morphine place conditioning. Administration of the selective D2 dopamine receptor antagonist raclopride (1.0 mg/kg) also prevented the enhanced response to morphine whereas the D1 receptor antagonist SCH-23390 (0.05 mg/kg) was without effect. These data demonstrate that sensitization develops to the conditioned rewarding effects of morphine. Furthermore, they indicate a critical role of δ-opioid and D2 dopamine receptor systems in the initiation of this phenomenon.

EFFECTS OF CTAP ON OPIOID-INDUCED REDUCTIONS IN CONDITIONED KEY-PECKING IN PIGEONS

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CTAP (D-Phe-Cys-Try-D-Trp-Lys-Thr-Pen-Thr-NH2) is a peptidic, cyclic somatostatin analog and a highly selective mu-opioid receptor antagonist that has been characterized largely in vitro. The present studies assessed the ability of intracerebrally administered CTAP to antagonize opioid-induced decreases in conditioned key-pecking in pigeons. Food-restricted pigeons were trained to peck a lit key under a fixed-ratio 20 schedule of food reinforcement. CTAP (1 μg) reduced the potency of the mu agonists morphine and fentanyl by one-third; CTAP (10 μg) did not further shift the rate-decreasing effects of morphine. A dose of 10 μg CTAP was needed to reduce DAMGO's potency by approximately 5-fold. CTAP (1-10 μg) did not antagonize the rate-decreasing effects of etonitazene. Still larger doses (100 μg) reduced response rates in all pigeons. Naltrexone (1 mg/kg, i.m.), an antagonist with highest affinity for mu receptors, produced a 5-10 fold reduction in the potency of morphine, fentanyl, and etonitazene to suppress conditioned responding in pigeons, but it did not antagonize CTAP's rate-decreasing effects. CTAP (1-10 μg) did not antagonize the response rate decreasing effects of the kappa-opioid agonist bremazocine, and the non-peptide, delta-opioid agonist BW373U86. Taken together, these findings suggest that under some conditions, CTAP acts as a mu-opioid antagonist in pigeons. Its profile of action is unlike other opioid antagonists.

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EFFECT OF NONPEPTIDE δ OPIOID RECEPTOR AGONIST TAN-67 ON THE MORPHINE-INDUCED PLACE PREFERENCE IN MICE

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The effect of 2-methyl-4α(3-hydroxyphenyl)-1,2,3,4,4a,S,l2,12 α-octahytroquinolino [2,3,3,-g] isoquinoline (TAN-67), a selective nonpeptide δ opioid receptor agonist, on the morphine-induced place preference was examined in mice. Morphine (1-5 mg/kg, s.c.) produced a dose-related place preference. In contrast, administration of TAN-67 (5-20 mg/kg, s.c.) did not result in a preference for either the drug- or vehicle-associated place. When TAN-67 (5-20 mg/kg, s.c.) was co-administered with morphine (1 mg/kg, s.c.), the morphine-induced place preference was enhanced dose-dependently, and this effect of TAN-67 was suppressed by the pretreatment with naltrindole (NTI; 1 mg/kg, s.c.), a nonselective δ opioid receptor antagonist, 7-benzylidenenaltrexone (BNTX; 0.05 and 0.5 mg/kg, s.c.), a selective δ1 opioid receptor antagonist, and naltriben (NTB; 0.05 and 0.5 mg/kg, s.c.), a selective δ2 opioid receptor antagonist. In biochemical study, neither morphine (1 mg/kg, s.c.) nor TAN (20 mg/kg, s.c.) alone modified dopamine (DA) turnover in the mouse limbic forebrain. However, co-administration of TAN-67 (20 mg/kg, s.c.) with morphine (1 mg/kg, s.c.) increased DA turnover in the limbic forebrain. This increase in DA turnover was suppressed by pretreatment with NTI (1 mg/kg, s.c.) and BNTX (0.5 mg/kg, s.c.) but not by NTB (0.5 mg/kg, s.c.). These results demonstrate that co-administration of TAN-67 with morphine produces the enhancement of morphine-induced place preference via activation of both δ1 and δ2 opioid receptors, suggesting that both δ1 and δ2 opioid receptors may modulate the morphine-induced rewarding effect, although this modulation by δ1 and δ2 opioid receptors may be elicited via different mechanisms, respectively.

CHANGES IN MORPHINE-INDUCED PLACE PREFERENCE AND ENHANCED DOPAMINE TURNOVER UNDER THE FORMALIN-INDUCED INFLAMMATION

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It has been reported that patients under severe pain were able to receive long treatment with no or only weak development of physical dependence. In the present study, we investigated the morphine-induced place preference and enhanced dopamine (DA) turnover under the formalin-induced inflammation in rats. Male Sprague-Dawley rats developed an inflammation upon the injection of formalin (2.5 %, 50 μl) into the plantar surface of right paw; the inflammation and hyperalgesia were recognized for about ten days. Morphine (2, 4, 8 mg/kg, i.p.) produced a dose-dependent preference for the drug-associated place in rats pretreated with vehicle. Surprisingly, under the inflammation, the morphine-induced place preference was markedly suppressed. Thereupon, the concentrations of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the limbic forebrain one hour after morphine (8 mg/kg, i.p.) or vehicle were estimated. The morphine-induced increase of DOPAC and HVA concentrations in the limbic forebrain was attenuated under the inflammation. These findings indicate that unilateral localized inflammation could suppress the rewarding effects of morphine by the attenuation of DA turnover, suggesting that the function of mesolimbic DA system might be changed by the inflammatory hyperalgesia.

METABOLISM OF 1-α–ACETYLMETHADOL (LAAM) IN HUMAN LIVER MICROSOMES: EFFECT OF P450 INHIBITORS

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1-α–Acetylmethadol (LAAM) is approved as a substitute for methadone for the treatment of opiate addiction. norLAAM, and to a lesser extent, dinorLAAM, are considered psychoactive metabolites. Little is known concerning their enzymatic formation. Human liver microsomes from four individuals were used to study LAAM and dinorLAAM N-demethylation. Product quantitation was by GC/MS. Incubation of LAAM with the microsomes resulted in norLAAM and dinorLAAM formation in a time, concentration, and NADPH-dependent manner. Greater than 5-fold variations in product formation were found between microsomes. A similar NADPH-dependence and variation between microsomes was noted when dinorLAAM formation from norLAAM was measured. When nor- and dinorLAAM formation from LAAM and dinorLAAM formation from norLAAM were measured, no significant inhibition of product formation was observed for the P450 isozyme-selective inhibitors (isozyme in parenthesis): ciprofloxacin (1A2, 100 μM), sulfaphenazole (2C, 100 μM), quinidine (2D6, 1 μM), or diethyldithiocarbamate (2E1, 100 μM). However, both LAAM and norLAAM metabolism were inhibited greater than 80% by ketoconazole (3A4, 3 μM). These results provide preliminary evidence for the involvement of P450 3A4 in the metabolism of LAAM.

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BUPRENORPHINE PHARMACOKINETICS: BIOAVAILABILITY OF AN 8 MG SUBLINGUAL TABLET FORMULATION

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Bioavailability from an 8 mg sublingual buprenorphine tablet was compared with that of an 8 mg/ml buprenorphine solution in 30% ethanol using pharmacokinetic and pharmacodynamic measures. The solution was used in pivotal clinical trials. A tablet will probably be used in treatment programs. Subjects were six men ages 23-42 (mean age ± SD, 27 ± 7 yr). The solution was administered in a 1 ml volume. The tablet was placed in the lateral sublingual space. Subjects held the solution in the sublingual area for five minutes and the tablet until subjectively dissolved (minimally 5 min; maximally 10 min). Plasma samples (10 ml) were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3.4, 6, 8, 10, 12, 24, 30, 36, and 48 hours after drug administration. Physiologic and subjective measures of opiate agonist effects were obtained at the same times as plasma samples. A gas chromatographic assay with electron-capture detection measured buprenorphine levels in plasma. Results show that AUC (unextrapolated 14.0 ± 6.4 vs 30.5 ± 11.2 hr•ng/ml) or an AUC-*to the same time* (14.0 ± 6.4 vs 28.7 ± 9.7 hr•ng/ml), and peak concentration (3.12 ± 0.50 vs 7.14 ± 2.80 ng/ml) were less after the tablet than after the solution (ANOVA confirmed by two one-sided [Schuirmann] tests/confidence intervals). The 8-mg tablet yields about 50-60% of the buprenorphine compared with the 8-mg solution. The rate of buprenorphine absorption is marginally slower from the tablet. The opiate agonist effects of buprenorphine were significantly less following the tablet.

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THE SUBLINGUAL BIOAVAILABILITY OF BUPRENORPHINE AT ANALGESIC DOSES

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This was an open, single dose, randomised four-way crossover bioavailability study of buprenorphine, 0.3mg IV and 0.2 mg, 0.4 mg and 0.8 mg SL with a one week washout between doses. Safety evaluations were undertaken after each dose. The study was carried out in 24 male healthy volunteers aged 19-39 (mean 27.7) years; 19 subjects completed the study. Blood samples, obtained up to 24 hours were analyzed using a partially-specific radioimmunoassay in which the antibody is known to cross-react with N-dealkyl buprenorphine. Mean peak plasma buprenorphine immunoreactivity concentrations of 0.28, 0.47 and 0.83ng/ml were attained at mean times of 96,91 and 91 minutes after administration of the 0.2 mg, 0.4 mg and 0.8 mg sublingual doses respectively and showed a highly significant extent of dose proportionality. Area under the curve (0-24 hrs) was calculated from the area to the time of the last detectable plasma concentration plus an estimate of the residual area up to 24 hours based on the terminal elimination rate. Based on mean AUC values the % bioavailability relative to the 0.3 mg intravenous dose for the 0.2 mg, 0.4 mg and 0.8 mg sublingual doses was 32%, 47% and 79% respectively, again showing dose proportionality. The best estimate of the fraction (F) of buprenorphine sublingually bioavailable was 0.35 obtained using data from the 0.4mg and 0.8mg sublingual doses.

EFFECT OF VARYING THE DURATION OF SUBLINGUAL BUPRENORPHINE EXPOSURE

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One of the inconvenient features of buprenorphine as an addiction treatment medication is its sublingual route of administration, and the possibility that variation in the mechanics of administration might alter pharmacological delivery. This study evaluated the effect of varying the sublingual exposure duration of liquid-formulated buprenorphine, with the goal of establishing the time required for optimal drug absorption. Healthy, adult volunteers with current sporadic opioid abuse, but not physically dependent, were enrolled for a three week inpatient study. The duration (0, 0.5, 1, 2, 4, and 8 min) of sublingual exposure to a fixed dose of buprenoprhine (8 mg) was varied in random order across six experimental sessions. Buprenorphine was prepared in 30% ethanol, and 1 ml was delivered sublingually using a Ped-Pod device. Physiological (pupillary diameter, respiration, heart rate, and blood pressure) and subjective indices were monitored for 15 minutes prior to and four hours following drug administration. In addition, oral pH was measured immediately prior to sublingual exposure, and multiple venous blood samples for measurement of plasma buprenorphine levels were obtained up to 24 hours post dosing. Preliminary assessment of data from seven volunteers suggests that the four and eight minute sublingual exposure durations were approximately equivalent with respect to the magnitude and the time of onset of subjective and observer ratings of positive drug effects but that shorter durations were associated with reduced buprenorphine effects. These data suggest that the standard sublingual exposure time to buprenorphine (5 min) is appropriate, and that shorter exposures may result in suboptimal absorption of this compound.

URINE TEMPERATURE DETERMINATION AS AN ALTERNATE METHOD FOR OBSERVED URINE TOXICOLOGY SCREEN IN DRUG TREATMENT

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Observed urine collection is the accepted standard for drug screening, but can be time consuming and intrusive. An alternative method to assess the authenticity of urine specimens that does not demand direct observation - urine temperature determination - is being evaluated in this study. Thirteen opioid dependent patients enrolled in a buprenorphine maintenance study in a medical clinic, submitted 276 urines for toxicology screening. Urine was collected in a paper cup and transferred into a plastic specimen container by the patient. Temperature of the urine was measured using a digital thermometer as soon as it was received. Urine specimen with temperature below 90°F, which did not register on the thermometer, was considered unacceptable and a new specimen was required of the patient. Of the 158 urines that were tested positive for illicit drugs (cocaine, opiates, benzodiazepam), the mean urine temperature was 93.07°F (+/-0.752) which is not statistically different from the mean urine temperature of 93.04°F (+/-0.722) of the 118 negative urines. We assumed that the drug-positive specimen was patient's authentic urine. As the temperatures of the drug-positive and drug-negative specimen were similar, we concluded that the drug-negative specimen was likely to be patient's authentic urine. We propose that urine temperature determination may be an alternate method for observed urine drug screenings which is less time consuming and more acceptable to patients and providers.

URINE TOXICOLOGY AS OUTCOME IN OPIATE CLINICAL TRIALS: HOW OFTEN AND WHEN?

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Clinical trials typically call for the collection and analysis of three urine samples per week (either on a random- or fixed-collection schedule) to detect changes in drug use patterns. Although the validity of various collection schedules has been described, the frequency of analysis capable of reflecting changes in drug use has not been explored. Data on over 16,500 urines collected from 225 subjects during a one year buprenorphine/methadone clinical trial were examined for the feasibility of establishing outcome by analyzing fewer urines per week for opiates. All samples were collected in the morning, either supervised or with the use of an FDA-approved tamper-proof collection system (Franklin Diagnostics), and analyzed for morphine using fluorescence polarization immunoassay (FPI) technology; a fixed percentage of FPI positive results were cross-confirmed by gas chromatography/mass spectrometry analyses. Percent-positive urines over the entire trial stongly correlated with percent-positive if only Monday samples (.94), Wednesday samples (.94), or Friday samples (.93) were analyzed. Further, day of week was not a significant correlate of opiate positive or missing urine samples. Twenty percent of urines collected on Monday morning were opiate positive, as were 20% of those collected on Wednesday and 22% of those collected on Friday; 13% of samples were missing across day of the week. We conclude that detection of opiate use remains relatively constant across day of the week and that analysis of one urine per week appears to be an adequate and cost-saving alternative to describe medication efficacy in terms of urine toxicology.

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DOUBLE-BLIND CONTROLLED DETOXIFICATION FROM BUPRENORPHINE

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When opiate dependent patients are receiving buprenorphine (B) daily, it is imp&ant to know how difficult it is to detoxify such pts. As one of 12 NIDA-sponsored multicenters, clinical trials of B in treatment of opiate dependence, 23 out of 60 pts who initially entered the program completed both the parent and extension protocols. The first 14 pts were randomized into two groups, rapid detox or gradual detox in a double-blind design. The rapid detox is 8 mg B for four days, 4 mg for four days, 2 mg for four days, and 1 mg for two days, followed by placebo for a total of 12 weeks. Seven pts were on the rapid detox schedule. There were many complaints from all pts. All experienced muscle aches and the majority had lengthy insomnia. Withdrawal symptoms of nausea, vomiting, rhinorrhea and sweating were also occasionally reported. Even with supportive medications (clonidine and promethazine) the pts assigned to rapid detox protocol continued to experience prolonged withdrawal symptoms. Five of the pts dropped out during the placebo period and all of them went back to using narcotics. Two completed rapid detox and remained narcotic free. The gradual detox is b 8,4,2,1 mg for two weeks each followed by placebo for a total of 12 weeks. Seven pts were on the gradual detox schedule. There were minimal complaints on the gradual detox. Three dropped out after eight weeks. Two went back to using narcotics, one remained drug free. Four completed the gradual detox and three of the four were narcotic free. The remaining 9 pts completing the parent and extension protocols can only enter the rapid detox schedule. All completed the two weeks rapid detox schedule. Five experienced muscle aches, diarrhea, nausea and insomnia. They all returned to narcotics. Four were drug free, but, it should be pointed out that these pts were on lower doses of B. Nevertheless, out of 16 on rapid detoxification, six were narcotic free compared to 5 pts out of 7 on gradual detox. In short, pts did poorly on rapid detox from B. Conclusion of this controlled detox is the slower the schedule of detox (56 days on active buprenorphine) the better the results.

CHRONIC PAIN AMONGST OPIOID ADDICTS IN BUPRENORPHINE DETOXIFICATION TRIALS

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One frequently heard complaint amongst opioid addicts is that chronic pain (CP) is driving their dependence. This retrospective study examined the prevalence of CP amongst patients seeking treatment for opioid dependence. Review of medical records from 105 consecutive admissions to our outpatient buprenorphine detoxification programs in 1991-1994 indicated that 42% had CP (*i.e.,* chronic back or neck problems). Age of onset of CP was compared with age of onset of opioid abuse, and the CP subjects were further divided into two categories: those whose opioid abuse preceded their CP (n=33) and those whose CP preceded their opioid abuse (n=8). No differences were noted between any of these three groups in Beck Depression scores, education, or Addiction Severity Index scores. However, those whose opioid abuse preceded their pain were more likely to be male and older than those without pain. Those whose CP preceded their opioid abuse were less likely to be single, employed, alcohol drinkers, or intravenous drug users than either of the other two groups. Throughout treatment, three weekly urine samples were obtained from all subjects and screened for various drugs. Males whose opioid abuse preceded their CP were more likely to be positive for opioids, methadone, and benzodiazepines than either of the other two groups. No significant differences in drug-positive urines were noted for females. Individuals with CP, regardless of its onset in relation to opioid abuse, tended to remain in treatment longer. Thus, while CP is prevalent amongst opioid-dependent individuals, data from our population suggest that CP is not a precipitating factor in the development of opioid dependence nor an impediment to treatment response.

BUPRENORPHINE DEPENDENCE AMONG INJECTING DRUG USERS IN MADRAS CITY, INDIA

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Buprenorphine has been marketed in India since 1987 as a prescription analgesic. This study reports on the widespread abuse of buprenorphine in Madras City similar to that seen in many parts of India. A study cohort of male injecting opiate users was recruited between May 1992 to August 1992 by street outreach for an HIV preventive intervention. Of the 250 enrollees 96.4% had used buprenorphine at sometime in their lives, 73.6% had used in the past 30 days and 44.4% met DSM III-R criteria for buprenorphine dependence. About one fifth of the sample initiated opiate drug use with buprenorphine and were continuing to use it at the time of recruitment. After 18 months, 69.6% of the 161 persons for whom follow-up is available were dependent on buprenorphine. At follow-up, a sample of sixty-eight injecting opiate users who agreed to an inpatient detoxification and treatment were evaluated using the Addiction Severity Index (ASI) and an opiate withdrawal rating scale, covering both objective and subjective symptoms. During the first 30 days after admission, the buprenorphine injectors had significantly less intense objective withdrawal symptoms; between 30 to 60 days after admission, they complained of more low level opiate withdrawal symptoms than the heroin injectors. The role of buprenorphine in the transition patterns of mode of administration among opiate users is discussed. The preference for buprenorphine among opiate users in a natural setting in India raises the possibility that increased familiarity and availability of this drug such as use for heroin dependence treatment may increase its illicit use.

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BUPRENORPHINE'S PHYSICAL DEPENDENCE POTENTIAL: ANTAGONIST PRECIPITATED WITHDRAWAL

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Buprenorphine (BUP) is a long-acting partial opioid agonist with demonstrable efficacy in the treatment of opioid dependence. One advantage of BUP over methadone and LAAM is its reported low physical dependence profile, attributable to BUP's slow dissociation from its receptor. However, there has been little systematic work to characlerize the amount of physical dependence produced by BUP. In the present study, seven opioiddependent volunteers maintained on 8 mg sublingual BUP were challenged with placebo, naloxone (10, 3, 1, and 0.3 mg/70 kg i.m.) or naltrexone (3. 1. and 0.3 mg/70 kg p.o.) 14 hours after their daily BUP dose. Challenges were scheduled twice weekly, with a minimum of 72 hours between them. Both naloxone and naltrexone precipitated dose dependent withdrawal, as evidenced by changes in subjective and observer measures. Significant precipitated withdrawal occurred at 10 and 3 mg i.m. naloxone and 3 mg p.o. naltrexone following a delay consistent with the oral route. These results are consistent with low physical dependence potential because naloxone precipitates withdrawal at a much lower dose range (0.2 - 0.4 mg) in subjects maintained on methadone, a comparably long-acting mu-opioid agonist.

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EKG CHANGES DURING BUPRENORPHINE/METHADONE ADMINISTRATION IN OPIATE DEPENDENT INDIVIDUALS

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Objective: We examined EKG changes during the maintenance and withdrawal phases of methadone (M) and buprenorphine (B) administration. Design: EKG data were analyzed on street opiate addicts (N=37; n=6 females). All patients were admitted to a randomized double blind double dummy parallel group inpatient study. Six groups were given oral M or sublingual B for 17 days following a four day induction period: M 30,60 mg; B 2, 8, 12. or 16 mg. EKG data were collected during screening and weekly. **Results:** Statistically significant - although clinically unimportant - EKG changes were observed. Both QTc and PR intervals were reduced over time ($p<0.03$). There was a differential medication effect on changes in the QRS interval over time. The QRS interval was reduced over time with B groups, but increased over time with the M groups. **Conclusions:** In our study, both M and B did not cause clinically significant alteration in cardiac conduction.

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OPIOID DETOXIFICATION WITH BUPRENORPHINE ALONE OR IN COMBINATION WITH NALTREXONE

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Opioid abstinence, although the treatment modality most widely used for opioid dependence, is often followed by relapse within the first week of detoxification. The opioid antagonist naltrexone is effective in preventing relapse, but its use is limited by unacceptable withdrawal symptoms if initiated before seven to ten days of abstinence from opiates. A short buprenorphine taper is comparable to clonidine for opioid detoxification. Buprenorphine may blunt the intensity of naltrexone precipitated withdrawal, confering acceptability of transition to antagonist treatment during the detoxification process. The safety and effectiveness of buprenorphine combined with naltrexone was compared to buprenorphine with placebo in an inpatient double blind study. Opioid dependent patients (DSM-III-R criteria) were randomized (N = 54; males 67%, Afro-americans 75%, mean age 31.5 years). All received sublingual buprenorphine [B] (day 1: 4 mg; day 2: 6 mg; day 3: 4 mg; day 4 : 2 mg; days 5 - 8: 0 mg) and double blind naltrexone [N] or placebo tablets [P] daily. N was either administered on days 2 - 4 (BN2-4 Group; n = 17), days 2 - 8 (BN2-8 Group; n = 20), or not at all (group BP; n = 17). Average length of stay (LOS) was 6.5 ± 2.2 days, 35 patients (64.8%) completed (≥ 7 days) treatment. LOS and retention did not differ significantly between the groups. On day 2, the Clinical Institute Narcotic Assessment [GINA] score for opiate withdrawal was higher and more clonidine was required ($p<.05$) for patients in BN2-4 and BN2-8 Groups. Other self reported and physiologic measures of opioid withdrawal showed no significant differences between the groups. These results show that the combination of buprenorphine and naltrexone is a promising approach for short opiate detoxification. Further research is needed to define the optimal relative doses of buprenorphine and naltrexone for symptom control.

THE DEVELOPMENT OF BUPRENORPHINE-NALOXONE PRODUCTS FOR TREATING OPIATE DEPENDENCE

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The National Institute on Drug Abuse in collaboration with Reckitt & Colman (Hull, England) is currently developing a buprenorphine-naloxone combination product. Buprenorphine has been demonstrated to be safe and efficacious for treating opioid dependence. However, it is potentially subject to abuse although it is a partial agonist. In order to reduce the abuse potential, naloxone (a narcotic antagonist with low sublingual potency) at 1/4 dose of buprenorphine has been incorporated in the combination formulation. Two strengths of the tablet product, buprenorphine 8 mg/ naloxone 2 mg and buprenorphine 2 mg/naloxone 0.5 mg are being developed. The sublingual effects of buprenorphine alone (8mg), and in combination with naloxone 8mg and 4mg (a dose ratio of 1: 1 and 2:1) were studied in subchronic buprenorphine- maintained subjects by Jones *et. al.* (1993). The results indicate that no detectable differences in physiological and subjective effects were found between buprenorphine alone and the combinations when administered sublingually. Since the pharmacological effects of sublingual buprenorphine were not affected by the presence of an equivalent dose of naloxone, it is anticipated that the clinical efficacy of chronic dosing with combination will not be attenuated by the presence of naloxone at 1/4 the dose of buprenorphine. The parenteral effects of the combination of buprenorphine and naloxone at dose ratios ranging from 8:1 to 2:1 were investigated in subjects maintained on an intramuscular dose of 60 mg morphine per day (considered to be moderately-dependent). The subjects were challenged intravenously with morphine 15 mg, buprenorphine 2 mg, placebo, and the combinations of 2 mg buprenorphine with .25, 0.5 and 1 mg naloxone (buprenorphine: naloxone ratios of 8:1, 4:1 and 2:1) at two day intervals. At the challenge dose ratio of 4:1, significant opiate antagonist effects, bad drug effects, sickness and slight withdrawal, were reported by the subjects suggesting that the combination would be unattractive for IV abuse (Jones, R. and Mendelson J. this volume). Data so far suggest that the sublingual combination product would be of similar clinical efficacy as sublingual buprenorphine alone but with limited abuse potential. Future clinical studies planned include pharmacokinetic (PK) studies to characterize the PK parameters, and clinical trials to demonstrate the safety and efficacy of the combination product in a clinical setting.

THE EFFECTS OF NALTREXONE MAINTENANCE ON THE RESPONSE TO YOHIMBINE IN HEALTHY VOLUNTEERS: A PILOT STUDY

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Preclinical and human (Charney and Heninger, 1986) research suggests that opiate antagonists alter noradrenergic responsivity. The current study compared the change in responses to yohimbine after two weeks of treatment with naltrexone to the response after at least two weeks of treatment with placebo. After a week of placebo naltrexone treatment, five healthy subjects were randomized into a double-blind, placebo-controlled crossover with placebo or active naltrexone (50mg p.o. daily) on weeks two through four, and the converse condition for weeks five through seven. Subjects received challenges in a random, fixed sequence with active and placebo yohimbine (IV, 0.2mg/kg) on weeks 1, 4, and 7.

All five subjects described greater peak "nervous" after the active yohimbine-active naltrexone combination than after any other, and four of the five described greater peak "not like" sensations. Four of the five described increased sexual feelings after the active combination; and two of the three men developed longer lasting erections with the active combination than with yohimbine alone. The results are preliminary, but suggest that clinically-used naltrexone doses alter sensitivity to yohimbine. Altered noradrenergic sensitivity might contribute to naltrexone's side effect profile in different patient populations.

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YOHIMBINE INDUCES WITHDRAWAL AND ANXIETY SYMPTOMS AND INCREASED ACOUSTIC STARTLE RESPONSE IN METHADONE PATIENTS

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This double blind placebo controlled study in eight patients receiving 50-80 mg of methadone daily, measured withdrawal, craving and intent to use opiates, Panic Attack Symptom Scale (PASS), physiological responses (HR and BP), acoustic startle, MHPG and cortisol after stimulation of noradrenergic systems with yohimbine 0.4 mg/kg iv. Yohimbine produced elevation in withdrawal as well as in PASS scores. Primarily somatic PASS symptoms were elevated (hot/cold flashes, muscle aches, muscle twitching, urinary urgency, and tremors) as opposed to "fear" symptoms. Craving was also elevated (ANOVA: yohimbine by time: df=2,7; f=3.6; p=.03). Blood pressure, heart rate, startle response, MHPG and cortisol also increased after yohimbine. Eighteen normal controls also showed increased PASS, heart rate, blood pressure, startle response, MHPG and cortisol after yohimbine. Compared with normal subjects, methadone patients had an increase in PASS score approaching significance (p=0.08). There was an increase in fear symptoms in methadone patients. Methadone patients also exhibited a greater increase in systolic pressure. (ANCOVA for baseline difference: yohimbine by time by methadone: df=3,23; f=3.01; p=0.04). Methadone patients had a greater startle response (n=12) (yohimbine by methadone: df=1,1; f=4.31; p=0.05). Methadone patients also had lower MHPG and higher cortisol levels. When corrected for baseline (by ANCOVA) the main effects of methadone and yohimbine on cortisol remained significant and there was a highly significant yohimbine by methadone by time interaction, indicating increased sensitivity of cortisol to yohimbine in the methadone subjects. When corrected for baseline the main effect of yohimbine on MHPG remained significant but methadone main effect and interaction were not. This study emphasizes the sensitivity of opiate dependent patients to noradrenergic stimulation and also suggests a risk for relapse and for initiation or exacerbation of comorbid anxiety.

PROTOCOL TO FACILITATE NALTREXONE TREATMENT FOR OPIATE ADDICTION

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Seventy-nine (79) detoxified opiate addicts were inducted onto naltrexone. To augment the pharmacotherapy, subjects were randomly assigned to either: Standard Treatment (n=38) consisting of monthly medication monitoring and counseling referrals; or, involvement in the Matrix Model (n=41) manualized psychosocial treatment protocol. Matrix materials combine relapse, cue exposure, psychoeducation and other cognitive behavioral strategies into an integrated treatment experience. Data were collected at baseline, weekly during the six months intensive treatment phase and at 6 and 12 months. Data from this preliminary analysis indicated that patients receiving the Matrix protocol were retained significantly longer and had significantly better treatment effectiveness scores. Four of the seventy-nine subjects (5%) died from opiate related overdoses during the study period. Final results of the study will indicate if the improved in-treatment performance with the Matrix protocol is associated with improved follow-up status.

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THE RELATIONSHIP BETWEEN SPIRITUAL EXPERIENCE AND LENGTH OF SUBSTANCE ABUSE TREATMENT

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Studies have shown an inverse relationship between anxiety and spiritual experience. Kass (1991) found individuals who report higher levels of core spiritual experiences, as measured by the INSPIRIT-R Questionnaire, have lower levels of anxiety. Also, there is an established correlation between anxiety and substance abuse treatment outcome. Therefore, it would be expected that persons with a higher level of spirituality would be more likely to have a more favorable substance abuse treatment outcome. Spiritual experience was measured in 32 adult male and female opiate users applying for Naltrexone treatment. Anxiety levels were examined using the subscore measure of the SCL-90-R. Length of study participation was measured in days from date of admission to last clinic visit date. The relationship between spiritual experience and treatment length was examined for the entire sample and for specific gender and race subgroups. A significant negative correlation was found to exist between the spiritual index and length of treatment participation for African-American women. No signilicance was obtained for any other groups. This study suggests that a measure of core spiritual experiences may be a predictor of treatment prognosis, as measured by retention. Naltrexone treatment has generally shown low retention rates which could have affected these results. Further examination of this construct may facilitate the development of more effective treatment modalities.

OUTPATIENT CLONIDINE/OXAZEPAM DETOXIFICATION FOR OPIOID WITHDRAWAL: COMPLETERS CHARACTERISTICS

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There has been increasing attention upon appropriate matching of patients to treatment over the past several years. This study attempted to identify characteristics of completers of an outpatient opioid detoxification procedure. Out of 233 opioid-dependent applicants for outpatient detoxification with clonidine HCl and oxazepam; 167 initiated treatment and 65 completed (were inducted onto naltrexone). Completers were more likely to be married, to have had previous detoxification attempts, to be non-IV users, to have last used opioids other than heroin, to have used benzodiazepines in the 30 days prior to intake, and had gone a longer time since last opioid use prior to intake.

The small percentage (28%) of completers emphasizes the importance of selecting the most appropriate candidates. The results suggest the usefulness of stabilization of heroin users on methadone prior to detoxification, consideration of more liberal use of benzodiazepines along with clonidine, and establishing a period of opioid abstinence as a condition for beginning treatment. Moreover, because this procedure was not successful with anyone attempting their first detoxification treatment, it may be better to try alternative approaches first.

CORRELATION AMONG MEASURES OF NALOXONE-PRECIPITATED OPIATE WITHDRAWAL

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A secondary analysis of data from 19 subjects who had sequential naloxone challenge tests showed: 1) The ACTH response to naloxone was robust and followed a similar time course as other withdrawal signs. 2) In subjects who received the same naloxone dose consecutively, withdrawal severity progressively diminished, with greater pulse changes and subjective withdrawal during the first challenge compared with the second. 3) In the *initial* naloxone challenge of subjects not receiving active medication pre-treatment, only one outcome measure trended ($p<.10$) to correlate with another, whereas there were ten correlations when these subjects' lust challenges were used. Taken together, the findings suggest that a subject's initial naloxone challenge may be qualitatively different from a latter challenge.

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BENZODIAZEPINE USE AMOUNG OUTPATIENT BUPRENORPHINE DETOXIFICATION SUBJECTS

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This retrospective study examined the prevalence of Benzodiazepine (BZ) use and its relationship to other drug use amongst 134 (89 males and 45 females) opioid-dependent individuals (ODI) receiving buprenorphine detoxification. Urine samples were collected under observation and analyzed three times weekly for the presence of opioids via Enzyme Multiplied Immunoassay Technique (Syva Corp., San Jose, CA). Samples were analyzed for the presence of BZ, barbiturates (BARB), cannabinoids (THC), and cocaine (COC) on one randomly chosen day per week. Results indicate that BZ users represented more than three quarters of the subjects (77%) and that 39% of all samples collected tested positive for BZs. A comparison was conducted to evaluate the relationships between BZ use and other drug use. BZ use was positively correlated with BARB use ($r=.2813$, $p < .001$), but not with THC or COC use. Additionally, females tended to use more BZ and BARB than males (43% and 14% vs 37% and 3%, respectively), Subjects were further divided into three groups: chronic-BZ users (>50% BZ-positive urines) sporadic-BZ users (1%-50% BZ-positive urines) and non-BZ users (0% BZ positive urines). Comparisons showed that chronic-BZ users had a tendency to use more BARB and COC than non-BZ users (11.38% and 18.07% vs 4.99% and 11.77%, respectively). Additionally, chronnic-BZ and sporatic-BZ users tended to spend more weeks in treatment than non-BZ users (18.65 and 11.94, $p < .05$). These results suggest a high prevalence of BZ use during buprenorphine detoxification trials. Further, continued use of BZ appears IO increase non-BZ drug use and treatment retention during outpatient buprenorphine detoxification.

PERSISTENT LEVELS OF INJECTION-RELATED HIV RISK AMONG NEEDLE EXCHANGE CLIENTS

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This study compares levels of HIV risk behaviors across three samples of needle exchange clients in San Francisco as a way to examine the trends within the needle exchange population. Three cross-sectional samples of injection drug users were chosen randomly and interviewed at needle exchange sites in 1990 (n=50), 1992 (n=114) and 1993 (n=125). All three samples had similar demographic characteristics. The 1993 group had a mean age of 40, and was 22% female, 59% white, 23% African-American, and 10% Latino/a. The other groups did not differ significantly. Heroin was the most common drug of choice (66%). In all three groups, the majority of people use the exchange at least once a week (63%) and have been exchanging for over six months (73%). Risk behaviors most clearly targeted by the needle exchange program appear to be decreasing over time, with significant decreases both in needle sharing occasions in the last 30 days, and in repeated use of syringes. However, 'indirect sharing' practices such as sharing of rinse waler, cotton or cookers remain at nearly constant levels. In the 1992 and 1993 samples, clients were also asked about sexual behaviors. Of those who were sexually active in the past 30 days (1992, n=74; 1993, n=64), two-thirds reported no use of condoms. While needle exchange may be an effective strategy for reducing HIV transmission among injection drug users, there is a need to develop additional interventions specifically targeting indirect sharing and sexual risk behaviors.

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METHADONE CLIENTS COMBINING DRUGS AND SEX USE MORE DRUGS

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IV drug abusers have demonstrated widespread decreases in HIV needle risk behaviors. Unfortunately, decreases in sexual risk behavior have been less impressive. In order to understand better the link between drug use and sexual behavior, IDUs who were enrolled in a methadone treatment outcome study were asked at the 24 month follow-up the percentage of time they combined various sexual behaviors and drug use during the prior six months. Data are reported for monogamous, heterosexually active males (n=106) and females (n=62). Using illicit drugs shortly before or during vaginal intercourse more than 25% of the time was reported by 41.5% of the males and 40.3% of the females. Those combining sex and drug use report more frequent use of heroin and cocaine. Even when individuals who report very high frequency of drug use are eliminated from the analyses, higher heroin use levels are reported by both males and females who combine sex and drug use. Females combining sex and drug use were more likely to identify sex as being more pleasurable under the influence of drugs. A similar association was not observed for males. Males and females who believe sex is more pleasurable under the influence of drugs reported higher levels of heroin use in the prior six months. The results have important implications for both drug abuse treatment providers and public health risk reduction workers. In order to help IDUs reduce both illicit drug use and risky sexual behavior, it will be important to understand the interplay between these behaviors for each individual.

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HIV TESTING IN A METHADONE CLINIC - TEN YEARS LATER

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In 1984-85, 94 patients at the New York VAMC were tested for HIV antibody. Fifty subjects (35-, 15+) received results in 1985-86 and emotional and behavioral impact was assessed in these and in a comparison group of 31 nontested subjects (81 total subjects). No major stress reactions occurred in any group but seropositives experienced higher levels of initial anxiety; seronegatives experienced relief, disbelief, and reported maintenance of risk reduction behaviors at 12 weeks. Anxiety about being infected increased in non-tested subjects during the course of the study. This population was studied again in 1994-5. Followup on 60 of 81 subjects was conducted and twenty-two participated in a followup study. Of the original 81 subjects thirty are known dead (52.6%), twenty-nine died of AIDS (8 non-tested, 13 positives, 8 negatives). Fourteen (93%) of seropositives are dead, only one in good health. Thirteen of the original 30 sero-negatives (47%) remain on methadone treatment, three are drug-free. All of these have been re-tested at least once. Eight 1985 seronegatives are known to have died of AIDS. AIDS anxiety, measured by the same scale used in 1985-6, is somewhat higher in the group than in 1986. Twenty-five (80 %) of the 31 nontested group are known to have been tested, (9 positive, 16 negative). Seven remain in methadone/LAAM maintenance and AIDS anxiety is also higher in this group than in 1986. The difference between surviving negatives and nontested 1985 subjects is primarily in terms of the time lag between last IV injection and the first interview in 1985. Those with a longer period of non-injection are the survivors. AIDS anxiety was also found to be higher in the survivors. All subjects report discontinued IV drug use and continued risk reduction behaviors. HIV testing has been integrated into the clinic, all 22 of the reporting individuals retested at least once. Concerns about contracting AIDS remains in a population that reports reduced risks, but is exposed to sick and dying friends.

AIDS KNOWLEDGE AMONG OPIATE-DEPENDENT PATIENTS VARIES BY AIDS EDUCATION EXPERIENCE AND RACE

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Opiate-dependent patients are at high risk of contracting and/or transmitting HIV. One necessary precursor to risk reduction is knowledge of the disease. This study assessed AIDS knowledge among opiate-dependent patients in treatment. We hypothesized that... 1) patients with a history of AIDS education will demonstrate superior knowledge compared to patients with no such history; and, 2) HIV+ patients will demonstrate superior knowledge compared to patients without the virus. Eighty-two opiate-agonist maintenance patients completed a voluntary, anonymous survey comprised of items assessing basic demographic characteristics, HIV test experience, HIV education experience, and 19 AIDS knowledge questions. Mean knowledge scores differed by AIDS education history, $t(56)=3.4$, $p<.001$. Contrary to the second hypothesis, data revealed that mean knowledge scores for patients with HIV disease did not differ from seronegative/untested patients $t(66)=0.2$, $p=0.9$. AIDS knowledge also differed by race with Latino patients manifesting the lowest mean score. These data suggest AIDS education efforts appear to be raising knowledge levels among opiate-dependent patients: however, such programs may need to address cultural differences.

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PSYCHOACTIVE DRUG USE AS A PREDICTOR OF HIV RISK AMONG SEXUALLY ACTIVE COLLEGE STUDENTS

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Introduction: College students often exhibit considerable social and sexual experimentation, including non-monogamous sex and psychoactive substance use. This study investigated the hypothesis that using alcohol and other drug use prior to sex was associated with greater HIV risk. Method: Unmarried, heterosexually active college students ($N=324$) were administered an anonymous questionnaire regarding sexual and drug use behavior in the previous 30 days, 12 months, and 5 years. Multiple linear regression analyses were used to predict the consistency of condom use during oral, vaginal, and anal sex enacted while under the influence of alcohol, marijuana, cocaine, and combined alcohol and cocaine. **Results:** Alcohol or marijuana use before or during sex in the last 30 days accounted for a significant proportion of the variance in inconsistent condom use during vaginal (adj. $R^2=.06$, $F=7.25$, $p<.002$) and anal (adj. $R^2=.19$, $F=13.28$, $p<.0002$) sex. Alcohol, cocaine, marijuana, and concurrent alcohol and cocaine use predicted inconsistent condom use during vaginal and anal sex, respectively, in the last 12 months (adj. $R^2=.15$, $F=12.56$, $p=.0002$; adj. $R^2=.06$, $F=5.08$, $p<.002$) and live years (adj. $R^2=.05$, $F=3.90$, $p<.002$; adj. $R^2=.71$, $F=78.19$, $p<.0002$). Condom use was rare during oral sex, and was unrelated to drug use for any time point. **Discussion:** The hypothesis that alcohol or other psychoactive substance use as a precursor to sex results in high levels of HIV risk behavior and may contribute substantially to the rapidly increasing incidence of HIV infection in this population was supported. Moreover, this pattern of risky behavior was likely to have preceded college entry. These data suggest that HIV prevention interventions for college and high school students should focus on increasing the salience of drug use as a facilitator of sexual risk behavior.

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HIV STATUS, RISK BEHAVIOR, AND AFFECT: A RETROSPECTIVE MATCHED CASE-CONTROL ANALYSIS

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This study was undertaken to further clarify the relationship between depression/anxiety and HIV status, and to examine risk factors related to HIV sero-status in substance abusing groups. It is a retrospective analysis of data collected from cocaine and opiate using subjects who were undergoing joint pharmacological and behavioral treatment at an outpatient substance abuse research clinic. Thirty-six subjects (28 males, 8 females), who tested positive for HIV at the time of initial intake, were matched with an additional 36 subjects who tested negative for HIV at initial intake and remained negative for HIV. Matching was based on study, condition within study, sex, age, race, and study retention status. Subjects were drawn from six studies: three opiate and three cocaine. Methadone dose level and visit frequency were the conditions matched within opiate studies. Fluoxetine dose level and visit frequency were the conditions matched within cocaine studies. The ASI, BDI, POMS. HAM-A, HAM-D, SCL-90, AIDS risk, and drug urine screen measures were analyzed for differences between HIV status and primary drug of abuse groups. Significant differences were detected on the POMS (Total and Depression scores), SCL-90 (Depression and Anxiety factors), ASI scales (Employment, Drug, Legal, Family/Social), and several AIDS risk behaviors. No differences were found for drug urine screens. For several measures, the HIV+ cocaine users' responses were more similar to the HIV+ and HIV- opiate users' responses than to the HIV- cocaine users' responses.

DRUG ACQUISITION AND HIGH RISK DRUG INJECTION

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Recent ethnographic research has identified injection-associated behaviors in addition to the direct sharing of a syringe that may facilitate HIV transmission. Among these behaviors is the dividing of shared or jointly purchased drugs as a liquid. This behavior may result in the transfer of HIV from one syringe to another if the syringe used for mixing and dividing the drug is contaminated with HIV. This study compares the frequency with which heroin and cocaine IDUs divide shared drugs as a solution, and it examines the relationship between this behavior and the social arrangements IDUs devise to acquire drugs. An instrument was designed and administered to active drug users in Denver (N=271). Results suggest that this injection associated behavior is common, that it occurs more frequently with some forms of drug acquisition than others, and that it occurs more frequently with heroin than cocaine. These results suggest the need to extend our research on "risk behaviors" to include the process by which specific acts become risky. In the case of injection associated risks, this includes investigating an injection process that begins with the strategies IDUs devise to obtain drugs and the methods they employ to prepare them for injection.

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SOCIODEMOGRAPHIC AND HEALTH STATUS CORRELATES OF HIV INFECTION IN DRUG USING WOMEN

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OBJECTIVE: The purpose of this preliminary research was to determine the sociodemographic and health status correlates of HIV infection among a sample of women drug injectors and crack smokers in East Harlem, NYC.
METHOD: Using targeted sampling, 109 drug using women were recruited from the streets of East Harlem, NYC. Drug use was verified by urinalysis. A structured interview was administered which included 1) sociodemographic variables; 2) history of: drug injection, drug treatment, trading sex for drugs and/or money, and incarceration; 3) history of hepatitis, gonorrhea, syphilis, genital warts, chlamydia, genital herpes, trichomonas, and vaginal candidiasis. HIV testing was conducted after the interview. Chi-square tests wee conducted to compare HIV infected women to non-infected women.
RESULTS: The sample was 59% African-American, 31% Puerto Rican, and 7% White; 27 women (25%) were seropositive, and 60% were crack smokers with no history of drug injection. Variables associated with HIV infection were history of: drug treatment, trading sex for drugs and/or money, and drug injection. Trading sex and drug injection were negatively correlated. Health status variables associated with HIV infection were history of: hepatitis, gonorrhea, syphilis, and vaginal candidiasis.
CONCLUSIONS: Ever trading sex, ever injecting drugs, and a history of sexually transmitted diseases are associated with HIV infection in drug using women. Multivariate statistical techniques with a larger sample size will be used to explore these relationships further.

RISK FOR HIV TRANSMISSION AMONG WOMEN CIVILLY COMMITTED FOR SUBSTANCE ABUSE TREATMENT

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Structured interviews about HIV risk behaviors were conducted with 21 women in a mandatory 30-day civil commitment program. Ages ranged from 25 to 54 years (n = 34.0 ± 8.1 SD). First alcohol use occurred during their teens or early twenties ($\bar{x}$ age = 14.6 ± 3.8), followed by onset of sexual activity and initial marijuana use. Regular drinking began at approximately age 17. DSM III-R criteria differentiated two subgroups. Regular cocaine use was reported most frequently, both alone (19.1%) and combined with alcohol (19.1%). 19.1% reported heroin dependence, and the remaining women were alcohol dependent. Over 85% claimed one main sexual partner, but 70% reported additional partners. Mean number of sex partners in the past five years was 4.0 ± 3.8, in the past year, 2.3 ± 2.0, and in the past six months, 2.1 ± 1.8. In the past year, 38% of the women were treated for STDs. Only 20% reported consistent condom use and another 40% said partners sometimes used condoms. Half claimed partners disliked condoms and that partners lacked confidence in condoms. Cleaning needles or using new needles was inconsistent. One-third reported needle sharing. Needle users also shared rinse water, cookers, and cottons, and "booting" or "milking" practices were common. Needle users rarely patronized shooting galleries, but crack cocaine users patronized crack houses. While 60% said they were HIV negative, 80% were concerned about past or future HIV exposure. Accordingly, involuntary treatment programs provide an opportunity "window" for addressing HIV risk behaviors that occur in conjunction with substance abuse.

PROBLEMS OF HIV-INFECTED SUBSTANCE ABUSERS ENTERING CASE MANAGEMENT

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Substance abusers with HIV disease are difficult to engage in case management. The data reported here are part of a randomized controlled trial of a case management intervention intended to improve the treatment of substance abusers with HIV infection. Specific aims are: (1) to identify key medical and social concerns of HIV-infected substance abusers entering case management; (2) to determine how self-reported problems of HIV-infected substance abusers entering case management vary as a function of demographic, medical, and psychosocial factors. Subjects are adult substance abusers with HIV infection, recruited at a hospital-based emergency department, inpatient units, and outpatient clinics. At the baseline interview, subjects were asked to identify the three problems in their lives that troubled them the most. Subjects' responses were categorized into ten areas: drug use, HIV-related issues, medical, psychological, relationship, housing, financial, transportation, employment, and legal difficulties. For the purpose of analysis these areas were collapsed into the following four domains of interest: psychological/relationship, substance abuse, medical, and community resource problems. Ninety six percent indicated psychological/relationship difficulties; 40% indicated substance abuse problems; 26% mentioned medical concerns, and 96% indicated community resource problems.

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PREDICTORS OF HIV RISK BEHAVIOR AMONG NON-INJECTION DRUG-DEPENDENT AFRICAN AMERICAN WOMEN

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Introduction: The relevance of the AIDS Risk Reduction Model (ARRM) to predicting HIV risk was investigated among indigent, heterosexual, non-injection drug dependent, African American women attending inpatient treatment. Methods: Subjects (N=80) completed interviews measuring ARRM and psychosocial mediating variables and HIV risk behaviors. **Results:** Subjects displayed high levels of sexual risk, including non-monogamous sex, repeated sexually transmitted diseases, high rates of exchanging sex for money and drugs, recurrent use of alcohol and other drugs proximal to sex, and infrequent condom use. Multiple linear regression analysis showed that non-monogamous sex in the 30 days prior to admission was associated with higher perceived risk of contracting HIV infection, more frequently exchanging sex for drugs, greater use of alcohol and other drugs proximal to sex, and lower socioeconomic status (SES). Logistic regression revealed that relative to condom non-users, condom users reported more frequent sexual communication with primary sex partners, higher SES, more sex partners, and more exchanging sex for money. Most subjects failed to label their behavior as placing them at risk for HIV, and were thus at a "pre-Labeling" ARRM stage. **Discussion:** Although several ARRM mediating variables significantly predicted HIV risk behaviors, psychosocial factors not included in the ARRM such as indigence, depression, using alcohol and other drugs proximal to sex, were typically better predictors. HIV prevention interventions among this sample should focus on instilling accurate perceptions of risk, reinforcing substance abstinence, and building sexual negotiation and other relevant skills. In addition to drug rehabilitation and job training to reduce financial dependence on partners, couple interventions may be particularly effective in reducing HIV risk related to infrequent condom use in committed relationships.

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ACCEPTABILITY OF VIRUCIDES AS AN HIV PREVENTIVE AMONG NON-INJECTION COCAINE DEPENDENT MEN

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Introduction: Spermicidal preparations of nonoxynol-9 (N-9) have been shown to inactivate HIV in vitro. Several characteristics (*e.g.,* inconspicuousness, lubricity) may render N-9 more acceptable for preventing HIV and other STDs than latex condoms, which are rarely used. As a prelude to evaluating the virucidahmicrobicidal efficacy of N-9 preparations in vivo, factors associated with their acceptability were examined. Methods: HIV seronegative, heterosexual, non-injection cocaine dependent men (N =60) attending a VA inpatient drug treatment program completed a structured interview battery, including questions regarding the desired properties of virucidal preparations. **Results:** Prior use of condoms lubricated with N-9 was reported by 51.7% of subjects, while use of N-9 preparations without condoms was reported by 26.7% of subjects. Acceptability of virucide use by female sex partners was reported by 67.9%. Preference for virucides relative to condom use was indicated by 65.0%. Desired attributes of an HIV preventive chemical barrier, in order of preference, were: does not interfere with sex (98.3%), is easy to apply (95.0%) and measure (93.3%), is similar to vaginal fluid (86.7%), does not taste bad (78.3%), is odorless (78.3%), is useable for extended hours (71.7%) prevents pregnancy (70.0%), is effective for having sex more than once (55.0%), allows pregnancy (51.7%), is not too slippery (45.8%) and is very slippery (40.0%). **Discussion:** These descriptive data suggest that, for this sample, virucidal chemical barriers have the potential for broader acceptability and use to prevent HIV infection than condoms. Preferred attributes included unobtrusiveness regarding the sexual experience, ease of use, and contraceptive potential. Variations in desired texture have implications for developing alternative virucidal preparations to appeal to different individuals.

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METHODOLOGICAL ISSUES IN CONDUCTING PHARMACOLOGIC INTERACTION STUDIES AMONG METHADONE-MAINTAINED PATIENTS

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For many injecting drug users (IDUs) maintained on methadone (METH), the efficacy of their dosage of METH is a dominating concern in their lives. Anecdotal evidence suggests that many of these patients will forego necessary therapies if they perceive the treatment may interfere with their METH. By virtue of the high prevalence of human immuuodeficiency virus (HIV) disease among IDUs, they may experience clinically relevant effects of drug interactions due to HIV-related therapies while enrolled in METH maintenance. Studies to determine the possible existence of drug-drug interactions with METH and HIV-related therapeutics are significant in these patients, both to alert clinicians to its likelihood as well as to allay any patient fears or perceptions. IDUs are frequently excluded from drug interaction studies. Their under-representation in this area of clinical research may lead to incorrect generalizations and conclusions regarding drug interactions. These interactions may possibly result in relapse to illicit drug use or non-compliance to medications concurrently prescribed for HIV-related conditions. We have successfully designed and conducted two drug-drug interaction trials with METH, one involving rifabutin and the other fluconazoole. We arc designing a series of inter-linked studies to improve the treatment of HIV-infected, METH-maintained patients. These studies will 1) answer fundamental *in vivo* pharmacological questions of METH metabolism utilizing isolated human liver microsomal preparations and 2) answer *in vivo* pharmacological questions regarding the interaction of METH and HIV-related therapies with focused, clinical drug interaction studies. We anticipate that these studies conducted in a multi-ethnic, METH-maintained population will yield clinically significant information for clinicians and their patients concerning the treatment of HIV-infected IDUs receiving METH therapy.

LONGITUDINAL HIV HIGH RISK BEHAVIOR IN METHADONE SUBSTITUTION PATIENTS

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Psychiatric comorbidity in drug abusers has been associated with poor treatment prognosis and increased risk of HIV infection. Given these findings, psychiatric comorbidity might impact on rates of change for a number of behaviors known to convey a high risk of HIV transmission (*e.g.,* drug injection, sharing injection equipment, high risk sexual behavior). Study participants were N=109 opioid abusers entering outpatient methadone substitution treatment. Complete data was available for N=69 at six months and N=50 at 12 months. Psychiatric and substance use diagnoses were made using the Structured Clinical Interview for DSM-III-R, completed two to four weeks following admission. Information on HIV high risk needle use and sexual behavior was assessed at baseline and months 6 and 12 using a structured questionnaire that employs a time-line follow-'back approach. The mean age of participants was 35.4 years, 55% were male, and 55% African-American or other ethnic minority. The most prevalent psychiatric disorders were antisocial personality (20%) and lifetime diagnosis of major depression (9%), with 44% of the patients having a lifetime comorbid psychiatric disorder other than substance use. Comorbid patients had higher rates of lifetime and current substance use disorders compared to non-comorbid patients. They also had higher rates of injection and sharing of injection equipment as well. as lower rates of condom use, and this relationship held true over the 12 month treatment interval. Appropriate psychosocial treatment with professionalized staff familiar with treating depression and personality disorder may be necessary to adequately treat this especially impaired group of patients.

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QUALITY OF LIFE IN A METHADONE MAINTENANCE PROGRAM

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Until now, the methadone maintenance treatments (MMT) have demonstrated their efficacy in the decrease of illegal opioid use, criminal activity, improvement of work status and, more recently, in the spread of HIV epidemic among opioid dependents. As opioid addiction, is a chronic disease, the effect of MMT on quality of life of the opioid patients under this treatment must be considered.

In the present work, the changes on health-related quality of life in a cohort of 135 opioid dependent patients (DSM-III-R) on methadone maintenance treatment (MMT) were studied. Health-related quality of life was assessed with the Nottingham Health Profile (NHP), just before to start the MMT, and at 1st, 3th, 6th and 12th months under the treatment. Sixty nine per cent of patients were male, most of them unemployed (61%), and involved in illegal activities (88%). All the patients were using heroine, most of them by intravenous route (90%), and 70% were HIV seropositives. After 12 months, 82 patients (61%) remained in the treatment program. An average improvement in the quality of life was observed mainly in the first month but maintained along the study (NHP overall scores baseline: 58±26, at first month: 40±26, and 12 months: 26±23, $p< 0.001$). There were no differences according to HIV status.

Patients on MMT improve dramatically their health-related quality of life. This improvement is independent of HIV status and precedes improvement in other indicators of MMT efficacy.

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MANIPULATIONS OF TYROSINE HYDROXYLASE mRNA WITH ANTISENSE OLIGODESOXYNUCLEOTIDES IN DOPAMINERGIC MIDBRAIN SYSTEMS

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Modulation of the transcriptional message of tyrosine hydroxylase (TH) was investigated in vivo in the nigrosuiatal dopaminergic (DAergic) system with different unmodified antisense oligodesoxynucleotides (ODNs), sense and mismatch ODNs controls. ODNs were infused (0.5 µg/0.5 µ1) unilaterally into the substantia nigra by osmotic minipump-systems over 14 days. Ipsilateral turning behavior was elicited after infusion of unmodified antisense ODN, while no significant asymetries were observed with sense, mismatch and vehicle infused rats. On the molecular and neurochemical level we observed no antisense effects on TH mRNA (in situ hybridisation, PCR), but a reduction of TH protein content in the substantia nigra (immunohistocliemistry, immunoassay) after antisense treatment. Microdialysis experiments revealed reduced extracellular basal DA release in the striatum ipsilaterally to the antisense infusion side. Furthermore amphetamine-induced DA release was significantly less when compared to the contralateral infusion side. Vehicle and mismatch ODN infusion into the substantia nigra was also without effect on THmRNA, TH protein content and striatal DA release. Our data show the potenlial of antisense targeting to further reveal relationships between neurotransmitter-related enzymes and behavioral performance. The possibility to selectively and discretely manipulate tyrosine hydroxylase concentrations and function will be a powerful tool to study pathological mechanisms in the DAergic nigrostriatal system.

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D_2 DOPAMINE RECEPTOR *TAQI* A GENOTYPIC DIFFERENCES IN EVENT-RELATED BRAIN POTENTIALS

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*Tuq*I Al gene markers at the D2 dopamine receptor (DRD2) locus have been found more frequently in drug abusers than in control subjects in several reported studies. To seek mechanisms through which variants at the DRD2 locus might modulate drug-abuse vulnerability, this study was designed to investigate central nervous system (CNS) factors, as reflected in electrophysiological measures, associated with *Tuq*I A variants. Event-related brain potentials (ERPs) were recorded from healthy male subjects with at least one copy (n =6) or with no copies (n=5) of the *Tuq*I Al form of the RFLP while they performed visual and auditory versions of the Continuous Performance Test (CPT) of sustained attention. The CPT has been shown to be sensitive to drug effects and to some forms of CNS pathology. The amplitude of the P300 component of the ERP reflects the allocation of processing resources, whereas its latency reflects the speed of information processing. ANOVA revealed significant *Tuq*I A-genotypic differences in baseline auditory but not visual P300 amplitude. In subjects with at least one copy of the Al form, auditory P300 was reduced in amplitude, as compared with P300 in subjects with no A1 copies. Analyses of ERPs recorded following placebo, 10- and 15-mg d-amphetamine revealed Genotype x Dose interactions on auditory and visual P300 amplitude. Data from this study provide preliminary evidence of possible baseline *Tuq*I A genotypic differences in electrophysiological indices of information processing, as well as preliminary evidence of *Taq*I A genotypic differences in response to *d*-amphetamine. These findings suggest a mechanism through which DRD2 genetic variation may contribute to differences in vulnerability to drug abuse.

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DOPAMINE D3 AGONIST 7-OH-DPAT ATTENUATES MORPHINE-INDUCED MOTIVATIONAL EFFECT

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We investigated effect of dopamine D3-receptor agonist, 7-hydroxy-N,N-di-n-propyl-aminotetralin (7-OH-DPAT), on morphine-induced motivational action and dopamine transmission in rats. Treatment with 7-OH-DPAT alone produced a significant place aversion, and this effect was not antagonized by pretreatment with D1-receptor antagonist SCH23390 and D2-receptor antagonist sulpiride. Morphine (4 mg/kg, s.c.)-induced place preference was prevented by pretreatment with 7-OH-DPAT. In microdialysis study, 7-OH-DPAT (1 mg/kg, s.c.), which produced significant aversive effects, decreased output of dopamine and DOPAC in the nucleus accumbens (N.Acc). Morphine (4 mg/kg, s.c.)-induced dopamine release in the N.Acc was significantly potentiated after the morphine conditioning as compared to the saline conditioning. This potentiation was antagonized by pretreatment with 7-OH-DPAT (0.1 mg/kg). These results suggest that 7-OH-DPAT may act on presynaptic dopamine autoreceptor, and may inhibit dopamine release and synthesis, resulting in producing place aversion and inhibition of morphine-induced reward. Furthermore, we found that the morphine-induced dopamine transmission in the N.Acc was potentiated by the morphine conditioning.

MORPHINE DOES NOT ALTER GABA UPTAKE BY CULTURED MESENCEPHALIC NEURONS

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The importance of GABA in opioid reinforcement prompted us to study opioid effects on development of mesencephalic GABAergic neurons. Dissociated mesencephalic cultures (E17) were maintained in vitro for nine days in serum free media (Neurobasal, Gibsco). Cells were plated at a density of 5.7 x 106 cells/mm2 in 24 well culture plates and exposed to morphine sulfate (MS) at a concentration of 10-6 to 10-14 M for the duration of the study. Following nine days in vitro, uptake of [3H] GABA was determined. GABA uptake was not significantly altered by addition of MS. Specific uptake blockers were utilized to discriminate between neuronal and non-neuronal uptake. These results indicated that, in the present culture system, only 2% of the total GABA uptake was neuron specific, the remainder being glial specific. This result suggested the presence of a large population glia in our cultures. This was confirmed by immunocytochemistry, which revealed that 39% of the cells in culture were GFAP immunoreactive. Addition of the anti-mitotic agent ARA-C did not enhance neuronal specific GABA uptake. Retinoic acid was added to cultures in an effort stimulated opiate mediated modulation of GABA uptake, however, MS did not alter uptake relative to controls. Finally, GABA release was ivestigated in order to determine if opioid effect on GABA levels was related to neurotransmitter release, rather than uptake. However, GABA release was unchanged in the presence of 10-6 M MS. We conclude that MS does not alter GABA uptake in dissociated embryonic mesencephalic cultures. This may be due to large population of astrocytic cells in our culture system.

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INTERACTIONS OF CHOLECYSTOKININ AND SOMATOSTATIN WITH μ AND κ ANTAGONISTS AND A μ OPIOID AGONIST IN THERMOREGULATION

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We have examined the effects of intracerehroventricular (ICV) injections of cholecystokinin (CCK-8) and somatostatin (SST) and the interactions of these neuropeptides with the selective opioid antagonists, CTAP (μ) and nor-BNI (κ) and the selective μ agonist, PL017, on body temperature (Tb) of the male S-D rat at normal ambient temperature (21 ± 0.5° C). ICV injection of CCK-8 produced short-lasting (15-60 mm), dose-related increases in Tb of 0.6-0.8° C in a dose range of 20-900 ng. ICV injection of lower doses of SST (1 μg and 2 μg) produced hyperthermia and a higher dose of SST (10 μg) caused hypothermia. The CCK (300 ng)-induced hyperthermia was blocked by pretreatment with CTAP (1 μg, ICV) and was potentiated with PL017 (1 μg, ICV). PL017 alone produced hyperthermia. CTAP alone did not change the Tb. These results suggest that CCK may increase the Tb through the direct activation of μ receptors or the release of endogenous opioids acting on the μ receptor. The hyperthermia elicited by a lower dose of SST (1 μg) was prevented by pretreatment with CTAP and not with nor-BNI (1 μg, ICV). Pretreatment with nor-BNI completely blocked the higher dose (10 μg) of SST-induced hypothermia. PL017 or CTAP did not change the hypothermic effect of that dose of SST. These results indicate that a lower dose of SST may stimulate the μ receptor, while a higher dose interacts with the κ receptor in regulation of Tb at normal ambient temperature. Thus, the present study supports the hypothesis that CCK and SST interact with the endogenous opioid system and contribute to the thermoregulatory functions of the μ- and κ- opioid systems.

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STUDIES OF *IN VITRO* PROCESSING OF DYNORPHIN A (1-17) IN HUMAN BLOOD AND IN RHESUS MONKEY BLOOD

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Comparative studies of dynorphin A [Dyn A (1-17)], biotransformation in human and rhesus monkey blood were conducted. Matrix-assisted laser clesorption/ionization mass spectrometry was used for the detection and identification of Dyn A (1-17) biotransformation products after addition of Dyn A (1-17) (0.59 mg/ml) to human (6 M, 2 F, average age 30.8 years, range 22-47) and rhesus monkey (3 F, average age 8.3 years, range 7-10) blood, *in vitro* at 37°C. The same general processing patterns were demonstrated in human and monkey blood. The amino terminal of Dyn A (1-17) was cleaved to generate nonopioid peptides, Dyn A (2-17) Dyn A (3-17) and Dyn A (4-17). of which Dyn A (2-17) was the major biotransformation product. Another selective cleavage site was between Arg(6)-Arg (7) with the formation of the opioid peptide, Dyn A (1-6) and the nonopioid peptide, Dyn A (7-17). Dyn A (7-17) was further processed to Dyn A (8-17) and Dyn A (9-17). The major biotransformation products were identified to be identical in both human and monkey blood, although there were some variations in relative amounts of products and in formation of minor products between human and monkey and among subjects. The study of temperature effect on Dyn A (1-17) biotransformation was carried out in human blood (n=3). No difference in processing patterns was observed for blood incubated at 25°C and 37°C, although biotransformation rate was higher at 37°C. These data suggest that rhesus monkeys may be a suitable model for further *in vivo* pharmacological studies. However, Dyn A (1-17) processing occurred at a faster rate *in vitro* in monkey blood than that in human blood, indicating that any use of rhesus monkey as a model for pharmacokinetic studies for humans will need to be carefully evaluated.

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INHIBITION OF ADENYLYL CYCLASE ACTIVITY BY OPIOID AND NON-OPIOID DYNORPHIN A PEPTIDES IN RAT CAUDATE PUTAMEN

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Adenylyl cyclase (AC) activity is used as one functional measure of opioid receptor-mediated signal transduction. The naturally occurring opioid peptide, dynorphin A_{1-17} (Dyn A,.,,), is thought to be the endogenous ligand of the (opioid receptor. It has also been shown to inhibit basal AC activity *in vitro* in rat caudate putamen (CPU) membranes (Claye *et. al.,* 1994). The processing of Dyn A_{1-17} and other shorter peptides (*e.g.* Dyn A_{1-13}) have been extensively studied in our laboratory. Primarily through the use of an *in vitro* assay using blood (humans and monkeys), rat whole brain homogenates, and in preliminary experiments using *in vivo* microdialysis in rat brain, the major biotransformation products of these dynorphin A peptides have been identified (Chou *et. al.,* 1994a&b; Yu *et. al.,* 1995). The purpose of this study was to determine the effects of Dyn A derived opioid and nonopioid products on basal AC activity as determined by measuring cAMP production in CPU membranes of naive Fischer 344 rats (n=6/group) using a cAMP radioligand binding assay. Our studies found that Dyn A_{1-17} Dyn A_{1-17} and one of its products, Dyn A_{1-17} each cause a concentration-dependent inhibition of AC activity. Dyn A_{1-6}, a product of both Dyn A $_{1-17}$ and Dyn A_{1-13} also inhibits AC activity. Unexpectedly, Dyn A_{2-17} a nonopioid peptide and major biotransformation product of Dyn A_{1-17} also shows a concentration-dependent inhibition of AC activity. Dyn A_{2-12} a nonopioid product of Dyn A_{1-13} also shows limited activity. However, Dyn A_{4-12}, a major nonopioid biotransformation product of Dyn A_{1-13} shows no inhibitory activity. These results suggest that Dyn A_{2-17} and to a lesser extent, Dyn A_{2-12} may be binding to a yet unidentified site that is also coupled to the AC enzyme.

CHANGES OF cGMP CONTENTS AND GUANLYLATE CYCLASE ACTIVITY IN THE SPINAL CORD IN THE MORPHINE DEPENDENT AND TOLERANT RATS

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It has been demonstrated that both nitric oxide synthase inhibitor and N-methyl-D-aspartate receptor antagonists can attenuate the development of morphine tolerance and physical dependence, which points to involvement of nitric oxide (NO) and guanlylate cyclase (GC) in the process of narcotic tolerance and dependence. The aim of present study was to investigate the cGMP contents and GC regulation by acute and chronic morphine administration. The soluble GC activity in the spinal cord was quantified by determinating the conversion of GTP to cGMP. The data are present as mean±SD (n=8) and statistical analyses were carried out using t-tests. cGMP contents in morphine acute treatment (10 mg/kg) and morphine dependent rats(doses increasing from 20mg/kg to 100 mg/kg for six days, bid, sc) were decreased from the control 45±9 pmol/g tissue to the 31±6 and 30±7 pmol/g tissue($p<0.05$), while the basal activities of GC were increased from the control 1.5±0.4 to the 2.8±1.4 and 2.9±1.1 pmol cGMP/min.mg protein ($p<0.01$). In addition, sodium nitroprusside (NO donating compound) stimulated GC activities were increased significantly from the control 17.5±5 to the 31±9 and 30±11 pmol cGMP/min.mg protein($p<0.01$), however, the ratios of activation of GC by NO were not different in each group. Naloxone (2mg/kg) caused the additional increase of cGMP contents (102±30 pmol/g tissue) and decrease of basal activity of GC in morphine dependent rats. In contrast, cGMP contents were increased, basal activity of GC unaltered, but sodium nitroprusside-stimulated GC activity enhanced in morphine tolerant rats (20 mg/kg, bid, for six days). Carbachol, a muscarinic receptor agonist, inhibited the basal activity of GC in control and morphine acute treatment rats, however, the inhibition of carbachol on basal activities of GC were not observed in morphine chronic treatment rats. The data suggested that GC-CGMP pathway also play a key role in narcotic tolerance and dependence as cAMP second messenger system, NO system, muscarinic receptor and u-opioid receptor may be responsible for the changes of GC-cGMP pathway induced by morphine at the spinal level.

EFFECTS OF SELECTIVE MUSCARINIC ANTAGONISTS ON MORPHINE TOLERANCE AND DEPENDENCE IN RATS

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The present study was designed to characterize the role of muscarinic receptor subtypes in the process of morphine tolerance and dependence using the muscarinic Ml selective antagonist pirenzepine and the muscarinic M2 selective antagonist methoctramine. Male Sprague Dawley rats were made dependence on morphine by subcutaneous injection of morphine two times a day for six days at doses increasing from 10 mg/kg to 50 mg/kg. After four hours from last injection of morphine, naloxone was given intraperatoneally to precipitate withdrawal. Ratings of opioid withdrawal signs were made every 15 minutes for one hour and body weight(g) losses were assessed over one hour, and analyzed using t-tests for correlated samples in the rats. Pretreatment with the methoctramine (0.01 mg/kg, 0.05 mg/kg, 0.5 mg/kg), the total ratings of naloxone precipitated withdrawal signs across the session were 10.1±3.2, 8.9±3.7, 2.3±1.4, respectively, which were different significantly from that of placebo (16.4±1.8). While body weight losses were 13.8±4.6, 11.5±3.6 and 6.5±3.9g respectively, which were less than the placebo (19±5.3g). The severity of naloxone-precipitated withdrawal after pirenzepine administration was similiar to the saline conditions. The morphine's antinociceptive effects were assessed by using hot-plate (HP) latency in rats. Infusion of methoctramine (0.25 mg/kg) for six days restored the sensitivity to morphine in rats that are tolerant as a result of six days of b.i.d. morphine injections. In contrast, administration of saline and pirenzepine (0.5 mg/kg) for six days did not significantly increased the mean HP latency of morphine-tolerant rats. Both methoctramine and pirezepine in doses did not alter the baseline HP latency. These observations showed that M2 receptor antagonists could prevent the naloxone induced withdrawal and reverse morphine (antinociceptive) tolerance, suggesting that M2 receptor play an important role in the processes of **narcotic tolerance** and dependence.

THE REINFORCING AND DISCRIMINATIVE STIMULUS EFFECTS OF GAMMA-HYDROXYBUTYRIC ACID (GHB)

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Gamma-hydroxybutyric (GHB) acid satisfies many of the criteria for consideration as a neurotransmitter including having specitic receptor sites, endogenous synthesis, and heterogeneous CNS distribution. GHB has been reported to be recreationally-used, to induce physical dependence, and to relieve effects from alcohol and heroin withdrawal. Preclinically, GHB has been shown to have antidopaminergic activity, to displace ^{3}H[MK-801] binding in brain membranes, and to have some *in vivo* effects similar to the classical antipsychotics. Because of its reported abuse liability, we evaluated GHB for its ability to support self-administration in rhesus monkeys. Because of its other reported pharmacological effects, we evaluated GHB for its ability to generalize to the heroin and PCP discriminative stimuli, and for its ability to antagonize the cocaine discriminative stimulus in rats. The results, to date, have indicated that under the tested experimental conditions the monkeys did not self-administer GHB (300 to 7500 µg/kg i.v.) above vehicle control rates, although they did self-infuse themselves at levels sufficient to produce signs indicative of sedation. Also, GHB did not fully generalized to the heroin nor to the PCP discriminative stimulus up to 300 mg/kg i.p., and did not effectively antagonize the cocaine discriminative stimulus when tested up to 200 mg/kg i.p. Other results and conclusions will be presented.

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DISCRIMINATIVE EFFECTS OF (+)-HA-966, A PARTIAL AGONIST OF THE NMDA-ASSOCIATED GLYCINE RECEPTOR

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The glycine site on the NMDA receptor complex is a target for the development of drugs for a host of therapeutic indications including drug abuse. For example, preclinical data suggests that tolerance and dependence to effects of a range of abused drugs may be prevented by functional antagonists of the glycine site. In the present experiments, the discriminative stimulus effects of R-(+)-3-amino-1-hydroxypyrrolid-2-one (HA-966), a low efficacy partial agonist, were explored. Male, Swiss-Webster mice (n=10) were trained to discriminate HA-966 (170 mg/kg, i.p.) from saline in a T-maze under which behavior was controlled by food. Other glycine partial agonists, 1-amino-1-cyclopropanecarboxilic acid (ACPC), and D-cycloserine, fully substituted for the discriminative stimulus effects of HA-966. The glycine antagonist, 7-chlorkynurenic acid, and antagonists acting at non-glycine sites of the NMDA receptor (NPC 17742, ibogaine, ifenprodil, dizocilpine) did not substitute for HA-966. Although the full agonist glycine did not substitute, this compound fully blocked the discriminative stimulus effects of HA-966. HA-966 did not substitute for dizocilpine in mice (n=6) trained to discriminate 0.17 mg/kg dizocilpine from saline. These data suggest that the discriminative stimulus effects of HA-966 are based upon its partial agonist actions at the strychnine-insensitive glycine site. Further, the lack of substitution of compounds with phencyclidine-like effects or sedative properties suggests that these side-effects may not be part of the subjective effect profile of glycine receptor partial agonists.

NMDA RECEPTOR ANTAGONIST BLOCKS THE EXPRESSION OF BOTH CONDITIONED PLACE PREFERENCE AND AVERSION

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Present study addressed the ability of the NMDA receptor antagonist (±)-CPP ((±)-3-(2-carboxy-piperazin-4-yl)-propyl-1-phosphonic acid) to block the expression of amphetamine (AMPH) conditioned place preference (CPP) or pentylenetetrazole (PTZ) conditioned place aversion (CPA) in male Wistar rats. During a four day conditioning period, daily injections of AMPH (1.5 mg/kg, s.c.), PTZ (15 mg/kg, i.p.) and their vehicles were paired with two distinctive compartments of shuttle box (balanced procedure). Two days after the last conditioning injection the post-conditioning test was held. Rats pretreated with saline (30 minutes prior to the test) showed significant preference for the AMPH-paired compartment or aversion of PTZ-paired one. Pretreatment with (±)-CPP (10-30 mg/kg, i.p.) dose-dependently blocked the expression of both CPP and CPA. These data are consistent with our previous findings that glutamate antagonists affect the expression of morphine CPP. Taken together with results of other studies, these data provide support for the hypothesis that NMDA antagonists exert a general influence on conditioned behavior by decreasing the motivational impact of both positive appetitive and negative aversive conditioned stimuli.

MECHANISM OF ACTION OF IBOGAINE: ROLE OF KAPPA OPIOID EFFECTS

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Ibogaine, an alkaloid extracted from Tabernanthe iboga, may be a novel, long-acting treatment for both opioid and stimulant abuse. Although there have been only anecdotal reports of long-term efficacy (up to six months after a single dose) in humans, studies in this and other laboratories have shown that ibogaine can decrease both morphine and cocaine self-administration for at least one day in all rats and for several days or weeks in some rats. In rats, ibogaine pretreatment (19 hours beforehand) also blocks morphine-induced dopamine release in brain and morphine-induced hyperactivity while, in contrast, it enhances similar effects of slimulants (amphemine and cocaine). Because ibogaine binds to kappa opioid receptors (2-4 μM affinity), we have begun to investigate the role of kappa opioid effects in mediating ibogaine's interactions with opioid and stimulant drugs. We now report that several of ibogaine's effects (*e.g.,* on morphine and cocaine self-administration, morphine-induced hyperactivity, cocaine-induced increases in nucleus accumbens dopamine levels) are mimicked by kappa agonists (U50,488 and spiradoline) and, to some extent, blocked by a kappa antagonist (nor-BNI). We also report that ibogaine is sequestered in fat, and that noribogaine, a likely metabolite, has a greater affinity for kappa receptors than ibogaine. It is proposed that ibogaine's long-term effects are mediated by slow release from fat tissue, conversion to noribogaine, and eventual agonist binding of both ibogaine and noribogaine to kappa opioid receptors.

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DETERMINATION OF IBOGAINE AND 12-OH-IBOGAMINE IN PLASMA BY GC/POSITIVE ION CHEMICAL IONIZATION-MS

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Ibogaine, an indole alkaloid from the *Tabernanthe Iboga,* has been presented as an effective treatment for cocaine, amphetamine and heroin addiction. A method is described in which ibogaine and 12-OH-ibogamine concentrations were determined using gas chromatography/positive ion chemical ionization-mass spectrometry (GC/PICI-MS). The analytical procedure involves a liquid-liquid extraction under basic conditions, followed by derivatization using MTBSTFA. The derivatization extracts were analyzed by GC/PICI-MS, using a Finnigan 9610 gas chromatograph equipped with a capillary column (DB1-15 M x 0.32 mm x 0.25 μm), and a 4500 mass spectrometer. The ions monitored in the study were m/z 311, 314 and 411, which corresponded to the protonated molecules (MH^+) for ibogaine, deuterated ibogaine and 12-OH-ibogamine, respectively. Drug concentrations were calculated against a calibration curve based on peak height ratios of analytes and the deuterated internal standard. Limits of quantitation (LOQs) were 10 ng/mL with a limit of detection of 5 ng/mL. Curves were linear from their LOQs to 1,000 ng/mL (r^2=0.995). Accuracy and precision of controls at 25, 100 and 300 ng/ml in human plasma were within 20% limits. Current studies are focusing on the suitability of the method for biological fluids from other species.

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RELATIONSHIPS BETWEEN NEUROTRANSMITTER RECEPTOR OCCUPANCY AND HUMAN SOMATOSENSORY EVOKED POTENTIALS (SEP)

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We have found that SEP characteristics differ between cocaine abstinent subjects and controls. Drugs of abuse, particulary cocaine, are thought to influence neurotransmitter activity associated with brain electrical activity. Demonstration of relationships between neurotransmitter and such brain activity may help to clarify sequelae of drug use on the brain. We present a method of simultaneously evaluating relationships between several neurotransmitter species and evoked potential characteristics and use these receptor occupancies of several antipsychotic drugs as a probe. The availability of Richelson's receptor affinity data for antipsychotic medications, and SEP data to right median nerve stimuli from 65 subjects receiving neuroleptics made it possible for us to examine relationships between estimates of recepror occupancy and SEP measures through the use of multiple partial correlational methods. We found SEP amplitude measures to be correlated with these neurotransmitters as follows: histamine (partial correlations - range -0.429 to 0.403), muscarinic (-0.356 to 0.424), 5-HT2 (-0.457 to 0.272) dopamine (D_2) (-0.296 to 0.360), 5-$HT1_a$ (-0.276 to 0.298), alpha 1-adrenergic (-0.227 to 0.298), and alpha 1-adrenergic (-0.223 to 0.285) receptors. Increased occupancy (blockade) of 5-HT_2, 5-$HT1_a$ or H_I receptors was associated with increased SEP amplitudes while D_2-like or muscarinic receptor blockade was associated with amplitude reduction.

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CLINICAL PHENOMENA AND STIMULANT SENSITIZATION

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Stimulant induced electrophysiological and behavioral sensitization are well elaborated in a precise pre-clinical body of data. Mounting clinical significance is being attributed to these data, based on clinical anecdotes, and not previously, on derived clinical findings. Such findings now exist. Four sets of clinical data are reviewed. I) Systematic data on cocaine abuse and paranoia in 50 consecutively admitted cocaine abusers that demonstrate cocaine paranoia follows a sensitization pattern, but not in all abusers II) Data on cocaine abstinence from a 220 subject "crack" sample that demonstrate a symptom factor structure which is not consistent with a sensitization model. III) Data on longitudinal relapse patterns from a large scale, multi-year crack study inconsistent with sensitization that indicate readdiction does not differ in pattern from initial addiction. IV) Data from treatment trials that demonstrate associations of mood and craving that are not consistent with sensitization. Evaluation of these systematic research findings rather than selected anecdote substantially alters conclusions drawn regarding the pertinence of sensitization to addiction and craving. We conclude that while sensitization provides a superbly fitting model for paranoia, it fails completely as a model advance fully explaining addiction.

SENSITIZATION TO COCAINE ARISES INDEPENDENTLY OF DRUG-INDUCED INCREASES IN DOPAMINE OVERFLOW

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Repeated exposure to psychostimulants, such as cocaine, results in an enhancement of their locomotor activating effects, a phenomenon referred to as behavioral sensitization. It remains unclear whether changes in mesocorticolimbic dopamine (DA) neurotransmission are critical for the initiation and maintenance of sensitization. Accordingly, the present study sought to characterize basal dialysate DA concentrations within the nucleus accumbens (ACB), 2, 12, or 22 days after the cessation of either repeated cocaine (20 mg/kg/day x 5 days) or saline (1.0 ml/kg/day x 5 days) treatment. Locomotor activity and extracellular DA levels in response to a subsequent cocaine challenge (20 mg/kg i.p.) were assessed at the same time intervals. Cocaine-pretreated animals exhibited an enhanced motor response to a cocaine challenge two days after cessation of cocaine treatment. The magnitude of this effect increased progressively over time. Basal DA levels were elevated two days after termination of cocaine treatment: at this time point, however, a blunted response of DA neurons to the cocaine challenge was observed. As the duration of withdrawal increased, basal dialysate DA concentrations gradually declined, whereas the response of DA neurons to cocaine progressively increased. By day 22 of withdrawal, a significant enhancement of cocaine-induced DA overflow was seen. The present data indicate that (1) repeated context-independent administration of cocaine produces substantial elevations in basal DA levels within the ACB during the early withdrawal period; (2) the magnitude of cocaine-induced alterations in DA overflow is inversely related to basal extracellular DA levels; (3) behavioral sensitization during early stages of cocaine withdrawal occurs independently of an enhancement of cocaine-induced DA overflow within the ACB. It is suggested that increases in both DA overflow and postsynaptic DA sensitivity develops during later stages of the sensitization process and may, therefore, be one of the mechanisms responsible for the long-term expression of cocaine sensitization.

5-HT_{1A} RECEPTOR MODULATION OF THE DEVELOPMENT AND EXPRESSION OF COCAINE-INDUCED BEHAVIORAL SENSITIZATION

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Serotonin (5-HT) systems have been shown to modulate some behavioral effects produced by cocaine (COC). We previously reported that the full and selective 5-MT_{1A} agonist 8-ON-DPAT (DPAT; 0.1 and 0.2 mg/kg, sc) enhanced COC-induced (10 and 20 mg/kg, ip) peripheral activity and decreased rearing and central activity; these doses of DPAT also decreased basal central and rearing activity, To further analyze the effects of this 5-HT_{1A} agonist, the development and expression of COC sensitization were assessed following pretreatment with DPAT (0.1 or 0.2 mg/kg, sc; N=8 rats/group) or saline (SAL) 15 min prior to an injection of COC (15 or 10 mg/kg, ip) or SAL twice daily for seven days. The profile of acute COC-elicited activity following pretreatment with DPAT on Day 1 was similar to that reported previously. By Day 7, significant and striking increases in peripheral, central and rearing activity were manifest in the DPAT+COC rats, as compared to SAL+COC controls. Therefore, DPAT pretreatment potentiated the development of COC-induced sensitization. However, this effect was apparent only when DPAT was on board. DPAT+SAL rats exhibited significant decreases in activity on Day 1 which were no longer evident by Day 7, suggesting that tolerance had developed to the acute hypomotive effects of DPAT; interestingly, levels of activity expressed on Day 7 in DPAT+SAL rats far exceeded those of SAL+SAL rats on either Day 1 or 7. Forty-eight hours after termination of pretreatment& DPAT+SAL rats (0.2, but not 0.1 mg/kg) responded more robustly to the first injection of COC than SAL+SAL rats; the magnitude of hyperactivity observed was similar to that seen in rats previously exposed to COC. Thus, chronic DPAT exposure may result in a “cross-sensitization” to COC. Overall, these data suggest that manipulation of the 5-HT_{1A} receptor has profound effects on COC-induced activity levels, thereby supporting the concept that this receptor may be an important substrate in the mediation of the locomotor effects produced by COC.

DAILY INTRA-A10 INJECTION OF GBR 12909, BUT NOT COCAINE, SENSITIZES ANIMALS TO A PERIPHERAL COCAINE INJECTION

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The mesolimbic dopamine (DA) system plays an important role in the development of behavioral sensitization to psychostimulant drugs such as cocaine. It has been proposed that the actions of psychostimulants within the A10 DA region, which is the origin of the mesolimbic system, is critical in the initiation of sensitization. This is based in part on reports which showed that daily injections of amphetamine into the A10 region induces a behaviorally sensitized response to challenge injections of amphetamine or cocaine. This study was designed to test whether daily intra-A10 cocaine could also induce sensitization. Male Sprague-Dawley rats received bilateral cannulae implants 1 mm above the A10 region one week before the start of an experiment. On day one rats received intra-A10 injection of vehicle or drug and motor activity was monitored. The rats received the same injection regimen on days two through four in their home cage. On day ten, all rats received saline (1 ml/kg, ip) injections and on day 11 all rats received cocaine (15 mg/kg, ip) injections. Daily intra-A10 cocaine (15 nmol/side) injections did nor produce an enhanced motor-stimulant to a peripheral cocaine challenge injection. Daily intra-A10 injections of the DA reuptake blocker, GBR 12009, did produce an enhanced behavioral response to cocaine. This enhanced response was not blocked by intra-A10 pretreatment with Iidocaine. The data suggest that repeated blockade of dopamine reuptake in the A10 region could induce sensitization. Also, cocaine may initiate sensitization by actions in other brain regions, in addition to the A10 region.

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BEHAVIORAL SENSITIZATION TO COCAINE FOLLOWING CHRONIC EXPOSURE TO INORGANIC LEAD

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Adult male rats were exposed to water containing 500 ppm added lead acetate (Group Lead), or water containing an equivalent concentration of sodium acetate (Group Control), for 30 days or 120 days prior to testing for the effects of repeated cocaine challenges on locomotor activity. Behavioral testing involved 14 successive daily one hour sessions in a Digiscan Activity Monitor, where after an initial 20 minute baseline period, one-half the animals from each exposure condition received a 10 mg/kg cocaine HCl challenge (IP), and one-half received a saline injection. On Day 15 all animals received only saline, and on Day 16 all animals received cocaine (10 mg/kg IP). The results indicated that the stimulatory effects of cocaine were augmented by repeated administration in both exposure conditions, but to a lesser degree in Group Lead animals. These data suggests that toxic chemicals in the environment may alter drug responsiveness.

CHARACTERISTICS OF COCAINE USERS SEEKING TO PARTICIPATE IN A COCAINE RESEARCH STUDY

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Cocaine users (n=266) seeking to participate in a cocaine research study were interviewed by telephone about their drug use, physical health and criminal history. The average age of respondents was 33 years. The majority of respondents (91%) reported that they currently used smoked cocaine; 21% reported current use of intravenous cocaine. Callers reported using the drug an average of four times per week and used an average of 3 grams of cocaine per episode of use. The majority of callers also reported using tobacco (89%) and alcohol (83%) regularly. Other findings of interest include: 70% of the entire sample reported having been tested for HIV, and 2% of those tested reported that they were positive for HIV; 49% of the entire sample reported having been convicted of a felony or gross misdemeanor, and 33% of this group reported their crimes to involve violence or the use of a firearm. Callers who were current or past users of IV cocaine were compared with callers who had never used IV cocaine. Comparisons showed that IV cocaine users were older, had more experience with other drugs of abuse, had higher incidence of current illness and hepatitis, and a higher criminal conviction rate than non-IV cocaine users. Controlling for the effects of age using a logistic regression technique eliminated the differences between these groups on measures of current illness and criminal history, but not on measures of experience with other drugs of abuse or incidence of hepatitis.

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AN ECONOMIC ANALYSIS OF THE RELATIONSHIP BETWEEN THE LEVEL OF ADDICTION AND USERS' SPENDING ON COCAINE

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Research on the association between cocaine users' spending and level of addiction is lacking. This analysis evaluates 1) *the relationship between addiction and self-reported value of cocaine used* 2) *the means used to pay/acquire cocaine,* and 3) *whether these means are reliable predictors of the value of cocaine used.* The NIDA-funded St. Louis' Effort to Reduce the Spread of AIDS project collected data on the value of cocaine used within 30 days prior to interview, Among the 436 respondents who reported lifetime use of cocaine, 50% reported current use. Respondents were 74% male, 91% African-American, 87% not *currently* married, and 75% unemployed or working part-time. Mean age was 32 years. Users reported spending an average of $678.07 on cocaine over the prior 30 days. Most users (87%) met DSM-III-R criteria for cocaine dependence. The baseline data show a strong correlation (.48) between the number of dependence symptoms and the reported value of cocaine used. To evaluate this relationship, a structural equation model with a latent variable for the amount of cocaine consumed was designed. Findings indicate that the frequency of cocaine used, employment status, making money illegally, trading sex for cocaine, and Adult Antisocial Behaviors were significantly associated with both cocaine dependence symptoms and spending. The model showed a good fit (X^2 = 10.69 with df = 4 and p = 0.03). The t-values for most of the explanatory variables (ranging from 2 to 9) were highly significant and the squared multiple correlation of the two structural equations are (R_1^2 = .69 and R_1^2 = .34) reasonably high. This confirms that quantity of cocaine used is the main cause for the strong correlation between addiction and spending.

WRAT-R READING PREDICTS IQ IN COCAINE ABUSERS

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We evaluated the relationships between WAIS-R IQ, WRAT-R reading score, demographic and drug use variables in 92 cocaine abusers, reported to evidence cognitive deficits, to develop prediction equations to estimate premorbid ability. Subjects' age was 31.8 (±6.7) and education was 12.4 years (±1.5). Subjects were abstinent for 9.5 days (±4.7) and had used an average of 4.3 (±6.3) grams of cocaine per week for six years (±3.8). Testing was done after 2 or more days on a locked research and rehabilitation unit. The results showed that WRAT-R reading (mean 87.2 ± 10.9) was correlated with IQ (Pearson's r, $p < .01$; Full Scale IQ = .43, Verbal IQ = .49, Performance IQ = .26). Demographic variables correlated with FSIQ [$p<.05$; education ($r = .21$) and age ($r = .23$)]. Abstinence and severity of use did not correlate with nor predict IQ. Only WRAT-R reading score and age accounted for 23% of the variance in FSIQ and 28% in VIQ. The regression equations are as follows:

FSIQp = (WRAT-R .319) + (age .274) + 51.19;
VIQp = (WRAT-R .366) + (age .237) + 48.83; and
PIQp = (WRAT-R .250) + 67.76.

Actual and predicted IQ scores were correlated significantly (FSIQ $r = .48$, $p < .001$; VIQ $r = .53$, $p < .001$; PIQ $r = .26$, $p < .02$) and did not differ based on within group t-tests. These data replicate the results of Wiens, *et. al.,* (1993), regarding the predictive power of the WRAT-R in normal adults with average or low average IQs and indicate that the WRAT-R reading score is a valid predictor of IQ in cocaine-dependent patients. Because word recognition ability appears to be resistant to deterioration in mild/moderate dementia, the WRAT-R reading test can be used to estimate premorbid functioning and gauge present cognitive deterioration in cocaine-dependent patients.

PSYCHOSTIMULANT NEUROTOXICITY: ARE THERE PERMANENT SEQUELAE TO "CRACK DANCING"?

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The prevalence of movement disorders in cocaine addicts is unknown and may be underappreciated. Daras *et. al.* (1994) report that addicts themselves have dubbed the choreoatbetoid movements (CM) associated with crack binges as "crack dancing". Fifteen inpatient male cocaine dependent (DSM IV criteria) patients were evaluated for CM with the Abnormal Involuntary Movement Scale (AIMS). Patients were excluded for a current or past DSM IV diagnosis of dependance on other substances but were not excluded for abuse of other substances with the exception of amphetamines. A group of ten matched normal controls who denied a history of drug dependance or abuse were also examined.

Differences between patients and normal controls in CM severity approached significance in the non-facial (limbs plus trunk) AIMS subscore ($t=2.02$, $p=0.055$). With abstinence, some decrease in the severity of CM was observed. However, in some patients, mild to moderate CM appeared to be permanent sequelae. Preliminary MRI evidence of both subtle and gross brain damage will also be presented.

Increased non-facial CM may be a marker for psychostimulant-induced basal ganglia neurotoxicity. Quantifying clinical and MRI markers of neuroloxicity associated with psychostimulant dependence could be useful in evaluating the impact of neurotoxicity on medication trial outcomes, and may suggest novel medication development strategies.

DEMOGRAPHIC, DRUG-USE, AND SYMPTOMATOLOGIC DATA AS PREDICTORS OF COCAINE-DEPENDENCE TREATMENT OUTCOME

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Early therapeutic failure is a common problem in the treatment of cocaine dependence. Dropout rates are high and the initiation of significant periods of abstinence is often difficult. Therefore, the identification of specific patient characteristics or indicators that could predict outcome with respect to outpatient cocaine dependence treatment would be clinically useful. In the present study, demographic, drug use, and symptomatologic data were obtained from cocaine- or cocaine/ethanol-dependent individuals presenting for dependence treatment. Subjects were identified from a retrospective review of admissions to an outpatient addictions treatment research facility over a one-year period. Discriminant function analyses were performed to assess whether particular variables (gender; heart rate; total scores from the Cocaine Selective Severity Assessment [an 18-item, clinician-administered cocaine withdrawal scale]; diagnosis of alcohol dependence; and amount of money, number of days of use, and number of days since last cocaine and alcohol use) were useful as predictors of therapeutic outcome as assessed by 1) retention in treatment for 30 or more days and 2) submission of three consecutive cocaine-metabolite negative urine samples during the first 30 days of treatment. Both analyses utilized the "direct" method which incorporated forced entry of all variables into the model. Evaluable data were obtained from 94 subjects for the first analysis, and from 54 who completed 30 days of treatment for the second analysis. The results indicated that the variables examined were fair to good pnedictors of which individuals were likely to attain one week of cocaine abstinence as assessed by the submission of three cocaine-metabolite negative urine samples in the first 30 days of treatment. The variables were also good predictors of which individuals were likely to complete at least 30 days of treatment but were not adequate to predict which individuals were likely not to complete treatment.

EFFECTS OF COCAINE WITHDRAWAL ON HUMAN MOTOR ACTIVITY

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Much behavioral work with cocaine in animals has used motor activity as the dependent variable, but there is little systematic data on human motor activity involving cocaine. We studied the motor activity of three cocaine-dependent (DSM-IIIR), African-American men (ages 33, 33, 26 years) during the first 18 days of cocaine abstinence on the closed DIR research ward. Subject's motor activity was recorded over 24-hour periods by wrist-watch sized activity monitors (Mini Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY) worn on their dominant wrist. These monitors record motor event frequency using an accelerometer, storing data in a microprocessor. Pilot work with staff indicated that these devices had adequate test-relest reliability, validly distinguished rest from motion, and gave a signal strength proportional to motion regardless of the plane of motion or its smoothness. Data from subjects was graphed at 3-5, 11-12, and 18 days of cocaine abstinence (two subjects at each time interval). Visual inspection of the data suggests no substantial qualitative differences in motor activity between subjects or over the course of cocaine withdrawal.

ACUTE COCAINE ADMINISTRATION REVERSES EEG SIGNS OF COCAINE WITHDRAWAL

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Abstinence from cocaine produces distinctive changes in EEG cordance, a putative measure of cortical metabolic activity (see Leuchter *et. al.,* 1994 for a description of cordance). In this study, we determined whether cocaine administration reversed those changes. Chronic cocaine abusers were admitted to a research ward and abstained from cocaine use for at least three days, confirmed by urine benzoylecgnonine. Acute administration of 23 mg or 40 gm IV cocaine rapidly reversed EEG frontal discordance characteristic of cocaine withdrawal. Over a period of 30 minutes, EEG frontal discordance gradually returned, and by the end of that period, discordance was more pronounced than before cocaine administration. EEG cordance changes were greater than those seen using other EEG measures, including power. FEG cordance may provide an instructive measure of neurophysiologic changes which is sensitive to cocaine withdrawal and intoxication. EEG measures may assist in guiding medication development for the treatment of cocaine abuse.

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QEEG SUBTYPES IN CRACK COCAINE DEPENDENCE AND TREATMENT OUTCOME

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This study demonstrates the existence of QEEG subtypes within a population of cocaine dependent adults. We have previously reported the existence of a distinctive quantitative EEG (QEEG) profile in such a population, which persisted at one and six month follow-up evaluations. In this study, 35 males, DSM III-R cocaine dependent, residing in a drug-free therapeutic community, were studied. Baseline QEEG evaluations were done live to ten days after last crack use. Using cluster analysis, two neurophysiological subtypes were identified at baseline: one characterized by significant deficits and of d and q activity and excess of *alpha,* and the second also showing deficits of d, but with more normal q and a absolute power, and excess percent power in the ß band. No significant relationships were found between QEEG subtype membership and any demographic or clinical characteristics, however, a significant relationship ($p \leq 0.003$) between subtype membership and length of stay in treatment (continued abstinence) was found. 81.3% of Cluster 1 members remained in treatment <20 weeks, and 84.2% of Cluster 2 members remained in treatment ≥20 weeks. Deficits of delta activity shared by both Clusters may reflect a long-term effect of chronic cocaine exposure, and can be interpreted in the context of a neuroadaptation hypothesis. Differences between the two Clusters may suggest different underlying neurophysiologic "traits", predisposing individuals to differential effects of cocaine.

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LABORATORY MODEL OF A COCAINE "CRASH" IN HUMANS

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The clinical literature suggests that intermittent cycles of repeated cocaine dosing, *i.e.,* binges, followed by abrupt cessation of cocaine use are associated with a distinct pattern of withdrawal symptoms and signs. Experienced cocaine users, including some maintained on methadone, completed a protocol investigating changes in behavior after the self-administration of cocaine. During sessions subjects could self-administer up to six doses of i.v. cocaine (32 mg/70 kg) or placebo. Both 2- and 3-binge cycle conditions were tested. During the 2-cycle condition, a cocaine self-administration/choice session occurred in the afternoon and again in the evening on two consecutive days, while during the 3-cycle condition, choice sessions occurred on three consecutive days. Self-reported effects were obtained during each session as well as the morning after each choice day and two no-drug days following each binge cycle. Based on the first eight participants, and in spite of large individual differences, several patterns of maximal morning-after scores were evident 1) Opiate Symptoms, abstinence symptoms, Beck Depression scores, and cocaine omission scores were greater during 3-binge cycles compared to 2-binge cycles, 2) Opiate Symptoms, abstinence symptoms, sleep disturbance, cocaine omission scores and ratings of "Anxious" remained elevated following 3-binge cycles, *i.e.,* abstinence, and 3) although abstinence symptoms, sleep disturbance, and ratings of "Anxious" increased during 2-binge cycles, these effects did not persist during abstinence. Thus, the repeated self-administration of cocaine in a binge pattern over several days produces subjective effects after the cessation of cocaine use that are dose-dependent, amenable to laboratory analysis, and may be described as a "crash."

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IMPROVING OUTCOME MEASURES. I. DEVELOPMENT AND VALIDATION OF URINE DRUG TESTING RULES TO PREVENT OVERESTIMATION OF COCAINE USE

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Urine drug testing provides an objective means of assessing recent cocaine use for patients in drug treatment programs and in clinical trials, but may overestimate drug use if the interval between testing is too short. Conversely, if the interval between drug use is too long, many episodes of drug use may not be detected. We developed a set of empirical rules for determining whether positive cocaine test results occurred as a result of new use or "carry-over" from previous use already detected. The rules were developed based on pharmacokinetic considerations of the excretion half-life of the cocaine metabolite, benzoylecgonine (BE; ca. 4-6 hours), urine collection intervals of 24-48 hours, use of an immunoassay (Abbott TDx Cocaine Metabolite assay) for semi-quantitation of drug test results, and the 300 ng/mL cut-off concentration used in qualitative testing. For validation, the rules were applied to test data collected from subjects residing on a clinical research ward. Subjects received cocaine by the intranasal, smoked and intravenous routes. All urine specimens were collected and analyzed by TDx for BE. Changes in BE concentration and metabolite/creatinine ratio from those of the previous specimen were calculated for each urine specimen. The new use rules were applied to approximately 1000 specimens at intervals separated by 24 and 48 hour intervals. Only a few instances occurred in which the new use criteria rules were incorrect in the diagnosis of new cocaine use and carry-over. The criteria for new uses appear to be valid under experimental conditions and may provide an improvement in the methods of estimating drug use.

IMPROVING OUTCOME MEASURES. II. APPLICATION OF URINE DRUG TESTING RULES IN A COCAINE TREATMENT TRIAL

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The effectiveness of cocaine abuse treatments can be monitored by self-reported drug use and objectively by qualitative or quantitative urinalysis; each method has strengths and weaknesses. Self-reported drug use is easily collected but has questionable validity. Qualitative urinalysis that indicates the presence of drug or metabolite at or above a designated cutoff concentration is an objective measure of cocaine use, though this testing method may be insensitive to decreases in cocaine use because of carryover positives. Quantitative testing may be more sensitive for detecting decreases in drug use, but adequate data are not available to evaluate its utility versus added expense. The usefulness of quantitative urinalysis for cocaine metabolite and creatinine correction techniques and the relationship between these data and self-reported drug use were assessed with data collected in a clinical trial (N = 37 subjects) of a contingency management behavioral treatment intervention. Criteria were developed to differentiate test results that represented new use from carryover. Results suggest: qualitative and quantitative tests show greater rates of drug use than self report: quantitative monitoring provides a means of differentiating incidences of new drug use from residual carryover and is more sensitive to decreases in cocaine use than qualitative tests; the identification of new use may help to reconcile differences between rates of drug use indicated by qualitative urine screens and self-report. Thus, quantitative testing appears to be a superior measure of cocaine use than either self-report or qualitative measures.

ADJUSTMENT OF BENZOYLECGONINE BY EXCRETED CREATININE: COMPARISON OF METHODS

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Urine benzoylecgonine (BE) levels are a primary outcome variable in pharmacological treatment studies of cocaine abuse, with 300 ng/ml established as the cut-off for a positive cocaine urine. However, BE levels are not generally adjusted according to the degree of urine dilution in these pharmacological trials. Thus, a study subject's urine BE level could fall below the 300 ng/nl cut-off level as the result of consuming a large volume of liquid. The purpose of this study was to examine BE values in relation to the 300 ng/ml cut-off when left unadusted or adjusted according to their corresponding levels of excreted creatinine (CN) in 1,909 urine samples obtained from 96 subjects (a subset of results from a multicenter trials of bupropion for the treatment of cocaine abuse). Four methods of BE adjustment were compared: (1) the division of BE level (ng/ml) by the milligrams of excreted CN, (2) the division of BE by the $\log_{10}$ of CN, (3) Thompson regression method (fitting of a regression of log BE with log CN, and then adjusting the observed BE values according to the regression line's intercept at the mean of $\log_{10}$ CN), and (4) Thompson method with constant slope (since the Thompson method requires a new slope for each study population, a constant slope value was substituted). The constant slope value was derived by adjusting data obtained during a fixed-dose cocaine administration paradigm with repeated measurements of BE and CN (Haberny *et. al.,* in press) according to the duration of time between cocaine use and urine sampling. In the absence of a gold standard, three criteria were used to compare the four methods of BE adjustment: (1) comparison of frequency of clean/dirty urines based on the 300 cut-off point. (2) comparison of frequency of false negative/positive urine based on study participant self-report, and (3) comparison of consistency of clean/dirty result across the different methods. The first two criteria revealed that adjustment of BE through division by $\log_{10}$ CN yielded significantly more clean urine values and two fold more false negative result based on self-report. This suggested that the formula BE/$\log_{10}$CN created values that were not comparable to the 300 cut-off point. The third criteria demonstrated that the Thompson method with constant slope disagreed most with the other methods. The lack of success with the constant slope Thompson method may reflect a slope value based on data from only four patients. Similar studies with a large number of patients are required to reevaluate this method. Further studies employing simultaneous urine and a suitable gold standard for the urine measures are required to evaluate the different methods of BE adjustment by CN.

RAPID- VERSUS SLOW-DOSE ESCALATION OF BUPROPION AND BROMOCRIPTINE FOR TREATMENT OF COCAINE DEPENDENCE

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Bupropion and bromocripline have been used separately for treatment of cocaine dependence. This eight week open-label outpatient study tested two medication schedules of the combination of bupropion (≤ 300 mg daily and bromocriptine ≤7.5 mg daily) with the goal of obtaining an enhanced therapeutic effect with less side-effects. The cocaine-dependent (DSM-IIIR) subjects were 69% male, 58% African-American, mean age 33.4 years, mean lifetime cocaine use 6.3 years. The first group (n=13) (Slow Dose Escalation [SDE]) received a slow dose induction and stayed a short time at the highest dose of both medications. The second group (n=13) received a rapid dose escalation (RDE) of both medications achieving the highest dose for a longer time. All patients in both groups received weekly individual slandardized counseling. No serious adverse events were reported. One patienl was discharged for a non-medication-related medical reason. Both groups had a significant decrease in self-reported cocaine use and craving. The RDE showed significantly longer retention time in treatment ($p < 0.05$), with no other significant differences between groups. These results suggest that the combination of bupropion and bromocriptine is safe and that a higher dose for longer Lime may be more effective for treatment of cocaine dependence. Further double-blind studies are needed to determine the effectiveness of the combination for this indication.

DOUBLE-BLIND OUTPATIENT TRIAL OF BROMOCRIPTINE FOR TREATMENT OF COCAINE ABUSE

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The dopamine agonist bromocriptine has been proposed as a treatment for cocaine abuse, but the limited existing clinical data is inconclusive as to its efficacy. We conducted a double-blind, randomized, 24-week outpatient clinical trial in 70 cocaine-abusing (DSM-III) men (86% African-American, mean age 34 years, 39 months of regular cocaine use [predominantly smoked], 16 days of cocaine use in prior month) with no other current substance dependence except tobacco (n=23). Subjects received four weeks of inpatient treatment, with induction onto bromocriptine (2.5 mg po tid) (n=35) or placebo (n=35) during the last two weeks. After discharge, subjects continued on medication with weekly group therapy. Both medication groups decreased their cocaine use and had low levels of depression and anxiety throughout the study. There were no significant group differences in retention in treatment, proportion of urine samples positive for cocaine (either in all subjects or in the 19 completers), adverse reactions, or reasons for leaving the study. These findings do not support the efficacy of bromocriptine in treating cocaine abuse, although it appears safe and well tolerated when used with a gradual dose escalation regimen.

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BROMOCRIPTINE DOES NOT ATTENUATE COCAINE USE OR CRAVING IN METHADONE MAINTENANCE PATIENTS

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Based on the theory that cocaine use and craving are driven by dopamine depletion, bromocriptine has been tested to treat cocaine withdrawal and cocaine dependence. We conducted a six-week study with one week of pre-treatment observation and five weeks of a randomized, double-blind placebo-controlled clinical trial of bromocriptine for DSM-15R defined cocaine dependence in methadone maintained male patients who were also beginning an intensive cognitive therapy. The bromocriptine dose was 2.5 mg po bid during weeks two through four with a step up/ step down dose of 1.25 mg po bid during weeks one and five.

The bromocriptine group (n=24) did not differ from the placebo group (n=26) in the decrease of self-reported cocaine use, the proportion of positive urine toxicology samples, the decrease in craving for cocaine, the increase in resistance to cocaine use or the improvement in mood symptoms between the pre-treatment baseline and the last week of the clinical trial. Both groups showed significant improvement in all self-reported outcomes during participation in the protocol. Side effect levels were modest: there were no differences between the bromocriptine and placebo groups.

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AMANTADINE IN THE TREATMENT OF COCAINE DEPENDENCE: A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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OBJECTIVE: This study evaluated the efficacy of amantadine in the outpatient treatment of cocaine dependence. **METHODS:** This double-blind, placebo-controlled trial involved 61 cocaine dependent subjects. Subjects received individual and group psychodlerapy together with amantadine 100 mg. (N=30), or placebo (N=31), three times a day, for three weeks. The medication was tapered during week four. A follow-up visit was conducted at week eight. Primary outcome measures were treatment retention and urine toxicology screens. Secondary outcome measures included the Addiction Severity Index (ASI), a cocaine withdrawal scale (CSSA), the Beck Depression (BDI) and Beck Anxiety Inventories (BAI), and cocaine craving measured on a 100 mm visual analog scale. **RESULTS:** There were no significant differences between the groups in treatment retention or in the percent of benzoylecgonine positive urines during medication or at follow-up. Secondary outcome measures showed significant declines, in both groups, in ASI composite drug and alcohol scores, BDI scores, and BAI scores. CSSA scores declined over time in both groups at a trend level. Craving scores did not decline significantly in either group. Only the ASI composite medical score showed a significant group by time interaction, with a significant worsening in the placebo group over the four weeks of medication. At follow-up, there were no significant group differences except for significantly lower ASI composite drug scores in the placebo group. **CONCLUSIONS:** This study does not support the efficacy of amantadine in the outpatient treatment of cocaine dependence. Some of the data suggests that the discontinuation of amantadine may have been associated with more cocaine use.

EFFICACY AND COMPLIANCE WITH CARBAMAZEPINE AND DESIPRAMINE VERSUS PLACEBO FOR COCAINE ABUSERS

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Craving for cocaine is associated with premature treatment dropout. Desipramine and carbamazepine have been reported to reduce craving. We assessed the efficacy of CBZ and DSI compared to placebo (PL) in reducing treatment dropout and positive urine toxicology. Subjects (N=146) were drawn from outpatient drug treatment at a community mental health center, met criteria for cocaine dependence, and were randomly assigned to DSI, CBZ or PL for an eight week trial which could be extended to six months. Subjects participated in ten hours group/individual treatment weekly. Observed urine samples were obtained weekly and analyzed for cocaine and five other abused drugs. Blood samples for DSI and CBZ were drawn bi-weekly; measures of craving were obtained weekly. Using an intent-to-treat model, survival analysis at 8 weeks, 16 weeks and 6 months indicated no difference between either drug and placebo in retaining subjects in treatment. Percent positive urine toxicology did not differ between either active drug and placebo. Analysis of blood level data using only subjects donating two or more samples, 74% of the population, suggests that subjects with blood levels of DSI >100ng/ml remained in treatment longer than those with lower levels; and subjects with blood levels of CBZ < 3 g/ml remained in treatment longer than those with higher blood levels. Results suggest the presence of a threshold of drug concentration related to therapeutic effect, and support the need for blood level monitoring to evaluate compliance with treatment and to determine drug efficacy.

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CARDIAC CHANGES OVER SIX WEEKS IN INPATIENT IV COCAINE ADDICTS RECEIVING COCAINE AND CARBAMAZEPINE

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Cocaine produces increased heart rate and blood pressure which acutely cause increased risk for cardiovascular events. Whether cocaine also produces subacute cardiac effects, which may put cocaine users at a chronically increased risk for cardiac events, remains unknown. This study retrospectively analyzed the occurrence of cardiac ectopy in 25 cocaine-dependent (DSM-IIIR) volunteers on a closed research unit over six weeks. **PROCEDURE:** Subjects (Mean (SD) age: 34.2 (6.0) years, cocaine use: 3.4 (5.2) g/wk, 8.6 (6.5) years of use; 21 men) without any serious physical or psychological impairment or other drug dependence participated in an investigational study of the effects of carbamazepine on response to IV cocaine. After baseline (Week), on MWF of Weeks 2-5. subjects received three doses of either 25 mg IV cocaine (2 days) or saline (1 day), delivered at 9 a.m., 11 a.m., and 1 pm. in random, double-blind fashion, with 24-hour ambulatory Holter Monitor recordings each session day. After Week 2, subjects received adjusted daily doses of carbamazepine (200-600 mg) or active placebo (diphenhydramine). A post-study period proceeded discharge. Hotter records were processed by computer software (Oxford Data Corp./Medifacts Inc.) for cardiac ectopy type and frequency, with physician verification. **RESULTS:** Over 6610 hours of continuous recording: two ventricular runs (3 and 12 beat), one ventricular couplet, Seven supraventricular runs, one idioventricular rhythm and no bigeminy were observed. No episode was accompanied by clinical symptoms. Nonparametric analysis found no significant ($p<.05$) association between any ectopy type and: Study Phase (Baseline, Session, Post-study), Session Week (Week 2-5), Medication Condition (carbamazepine vs. placebo), Drug Condition (cocaine vs. saline), or Drug by Time (9-3 p.m., 3-9 p.m., 0-3 a.m., 3-9 am,). For isolated premature ventricular contractions (2.4/24H), isolated supraventricular contractions (6.7/24H) and ventricular pauses (>2.0 sec, 0.1/24H), a repeated-measures ANOVA also found no significant effects. **CONCLUSION:** Healthy cocaine addicts show low baseline rates of cardiac ectopy which arc stable over several weeks, appear unaffected by low doses of cocaine, and are not highly predictive of risk for adverse cardiac events.

EFFICACY OF TWO DOSES OF TYROSINE IN RETAINING CRACK COCAINE ABUSERS IN OUTPATIENT TREATMENT

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Craving for cocaine is associated with premature treatment dropout among crack cocaine dependent patients. Diminished dopaminergic neurotransmission has been suggested as an etiology of craving. We wished to determine if the amino acid precursor of dopamine, tyrosine, would reduce craving and early treatment dropout. Subjects (N=50) were drawn from patients who enrolled in outpatient drug treatment at a community health center and met criteria for cocaine dependence. Subjects were randomly assigned to one of two tyrosine dosage levels (800 mg BID or 1600 mg BID) or matched placebo for a minimum eight-week trial. Subjects participated in ten hours of group and individual treatment weekly. Random, observed urine samples were obtained weekly and analyzed for cocaine and five other drugs of abuse. Analysis of variance demonstrated no difference among the two dosage groups compared to each other, or to placebo, in retaining subjects in treatment or in reduction of percent positive urine toxicology. These findings do not support a role for tyrosine in management of craving for crack cocaine, nor in reducing either premature dropout or continuing use of cocaine.

ACKNOWLEDGEMENTS:

Supported by NIDA #R18DA-06954.

A CONTROLLED TRIAL OF FENFLURAMINE IN COCAINE DEPENDENCE

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Objective: A controlled trial of fenfluramine 60 mg/day was conducted to determine its effectiveness in treating cocaine abuse in methadone maintenance (MMT) patients. Method: Balanced group double-blind, placebo-controlled, crossover design. Subjects received either fenfluramine (FEN) 60 mg/da *or* placebo (PLA) for a four week period, then received placebo for a one week single-blind washout, and then underwent a double-blind crossover to FEN or PLA for a second four week period. Subjects were 31 DSM-III-R secondary cocaine dependent MMT outpatients. Subjects were 58% female, 48% African American, 23% Hispanic, 23% White, and 6% other. Eighty-seven percent were HIV positive. Measures of cocaine use included quantitative urine benzoylecgonine (BE) levels. Results; *Median urine BE* was 26,972 ng/ml at intake; 30,084 ng/ml for the four weeks on PLA; and 27,064 ng/ml for the four weeks on FEN (NS). *Mean days of cocaine use* was 3.8 da/wk at intake; 2.2 day/week on PLA; and 2.0 day/week on FEN (NS). *Median dollars worth of cocaine used* was $90/week at intake; $38/week on PLA; and $35/week on FEN (NS). *Mean cocaine craving* was 12.2 (range 0-24) at intake, 7.3 on PLA and 7.2 on FEN (NS). One subject (5%) had to discontinue FEN prior to completion of the study due to side effects. Conclusion; Fenfluramine appears to be safe and well tolerated in cocaine dependent MMT patients. In this study, fenfluramine did not appear to be associated with reductions in cocaine craving or cocaine use in cocaine dependent, mostly HIV infected MMT patients.

ACKNOWLEDGEMENTS:

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EVALUATION OF PHENTERMINE AND FENFLURAMINE, ALONE AND IN COMBINATION, IN NORMAL VOLUNTEERS

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The combination of phentennine, a dopamine releaser, and fenfluramine, a serotonin releaser, has been shown in controlled studies to be an effective treatment for obesity. Recent clinical reports indicate that the combined effects of phentermine and fenfluramine may also be useful in the treatment of substance abuse disorders. Before wide-spread use of this combination can be implemented, its safety should be evaluated in controlled, double-blind studies. The present study was designed to evaluate the abuse potential of these drugs, alone and in combination, by characterizing their subjective and mood-altering effects in normal volunteers. Seven male and five female volunteers participated in an eight-session, double-blind study, in which each subject received acute doses of d-amphetamine (10 and 20 mg), phentermine (30 mg), fenfluramine (40 and 80 mg), phentermine (30 mg) + fenfluramine (40 mg), phentermine (30 mg) + fenfluramine (80 mg), and placebo. The order of drug administration was random, except that the high dose fenfluramine conditions were always last. Sessions were conducted in the laboratory two or three days per week. Subjects completed standardized self-report questionnaires and psychomotor tests before and at regular intervals after each drug administration. Phentermine produced effects that were similar to those of d-amphetamine (*e.g.,* increased ratings of arousal and drug liking). In contrast, fenfluramine produced different and apparently aversive effects (*e.g.,* increased ratings of anxiety and confusion). Phentermine reduced the apparently aversive effects of fenfluramine when the two drugs were given together. These results suggest that the combination of phentermine and fenfluramine would have a low potential for abuse.

ACKNOWLEDGEMENTS: This research was supported by NIDA grant DA02812.

HUMAN LABORATORY ASSESSMENT OF METHYLPHENIDATE (MP) EFFECTS IN COCAINE DEPENDENT PATIENTS

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This is a report of results obtained when 12 cocaine dependent patients received placebo and MP (15, 30, and 60 mg) doses under double-blind conditions in the human laboratory. All patients previously completed a double-blind outpatient treatment with methylphenidate (20 mg SR, b.i.d.) or placebo. They were included in this study if they required additional treatment. This was a dose ranging study to evaluate the safety and utility of using higher MP doses. Subjects received MP doses in an increasing series with placebo administered at the beginning and at the end of the series. Standard measures of physiological, performance, and subjective effects were employed. Sixty mg MP increased heart rate but no subject experienced any adverse cardiovascular reactions during the study. MP significantly increased visual analog ratings of feeling stimulated and jittery, as well as ratings on the amphetamine and the LSD dysphoria scales of the ARCI. Contrary to expectation, MP did not increase several measures of abuse liability (*e.g.,* drug liking, cocaine-high ratings from the visual analog scale, and the BG or MBG euphoria scales of the ARCI). Furthermore, methylphenidate did not increase or decrease subject ratings related to craving (*i.e.,* craving, urge to use, would use, and could refuse). These data indicate that higher doses of methylphenidate produce mainly dysphoic stimulant effects in this population of cocaine-dependent outpatients and therefore would not be expected to have therapeutic benefits in an *"agonist"*-type of therapy.

METHYLPHENIDATE (MP): AN ADJUNCT FOR COCAINE DEPENDENCE?

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Agonists, or "replacements", as adjuncts in treatment of drug dependence have utility. Methadone is a standard for this approach. There are few data for a stimulant 'replacement model'. Early reports by Khantzian, Gawin, Kleber, and Kosten using MP were contradictory and Grabowski *et. al.,* (1994) reported equivocal results.

Forty-nine subjects were enrolled and twenty-four subjects completed an eleven week *double blind placebo (PBO) controlled trial of methylphenidate,* preceeded by a two week stabilization period. Group assignment was randomized. Intake included psychiatric, medical, and a two day human laboratory evaluation (Thomson, Roache *et. al.,* 1995, CPDD). Subjects attended clinic Monday-Friday, receiving MP (5mg immediate+20mg sustained release[SR]) or placebo (PBO) at 8 a.m., and afternoon take home doses (20mg-SR or PBO) in MEMS bottles. Therapy sessions, self-report data, and EKG were conducted weekly. Urine screens were twice weekly.

Retention and cocaine use outcomes were equivalent for the two groups. No adverse effects were detected. The MP dose was sufficient to produced measurable "stimulant" effects ("more energy", "eating less") and complaints of "jitteriness", while PBO patients reported being more "drowsy". There was no increase in cocaine use or self-reported "craving". This suggests that concerns about "priming" are unwarranted. While there were no effects to justify safety concerns, neither was there evidence that MP is a clinically effective replacement for cocaine dependent patients. Human laboratory evaluation integral to clinical trials may expedite medication development. Medication with greater positive effect must be examined to further evaluate the 'agonist' model.

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FLUOXETINE IN THE TREATMENT OF COCAINE DEPENDENT METHADONE PATIENTS

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This was an open label, prospective, eight week study to evaluate fluoxetine's efficacy in reducing cocaine craving and use, in cocaine dependent methadone maintenance patients. Six subjects meeting the DSM III-R criteria for cocaine dependence were administered 20 mg of fluoxetine daily for two weeks, followed by 40 mg. daily for six weeks. Baseline measures included the Addiction Severity Index (ASI), a cocaine craving scale, and the Beck's Depression Inventory (BDI). The craving scale, BDI, and urine drug testing were administered weekly, and the ASI was repeated on completion of the study. The results showed a statistically significant reduction in the posttest ASI's Drug Use Composite Score using the Wilcoxon Matched Pairs Signed-Ranks Test. There was no significant difference between pre and posttest BDI. cocaine craving, and urine drug test results. Two patients' BDl, and ASI's psychological composite scores increased. Thus, while there were some individual differences in response to fluoxetine, it did not appear to be useful in diminishing cocaine craving and use in this study.

EFFECT OF ASPIRIN ON CEREBRAL PERFUSION DEFICITS IN CHRONIC COCAINE USERS: PRELIMINARY RESULTS

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Chronic cocaine use has been associated with focal deficits in regional cerebral blood flow (rCBF) which may be due to cocaine-related vasoconstriction and platelet activation and aggregation. Aspirin, an anti-platelet agent, may reverse these deficits. We have studied six cocaine dependent subjects (5 men, 1 woman; ages 23 to 36 years; median cocaine use 5.0 grams/week) who were all actively using cocaine at the time of their entry into this study. Subjects were treated with aspirin 325 mg daily for four weeks. 99m-Tc-D,L-hexamethyl propyleneamine oxime (HMPAO) and Single Photon Emission Computed Tomography (SPECT) were used to study rCBF within 72 hours of admission, and after two and four weeks of abstinence from cocaine and therapy with aspirin. rCBF was defined as activity in each region of interest normalized to peak activity in cerebellum. Preliminary analyses showed each subject to have multiple areas of cortical blood flow deficit at admission (rCBF < 72% peak activity in cerebellum) ranging in size from 0.6 cm to 3 cm. From baseline to week four, the mean increase in rCBF in areas of blood flow deficit was 10%, with the largest increases occurring in the fist two weeks of treatment ($p = 0.056$). There was marked heterogeneity in individual response of rCBF to abstinence from cocaine and treatment with aspirin. Work is underway to compare the effects of aspirin on cerebral blood flow to the effects of other medications which also inhibit platelet granule release.

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NEEDLE PUNCTURE CONTROLS FOR CLINICAL TRIALS OF ACUPUNCTURE

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In order to identify an appropriate needle puncture control for non-specific effects of needle insertion for use in clinical trials of acupuncture for cocaine addiction we conducted a single-blind study in which ten cocaine dependent subjects rated local and systemic effects of four auricular needle puncture configurations: “active” sites commonly used for addiction; “inactive” sites proximate to addiction specific sites; “active” sites not specific for cocaine addiction; and sites in the ear helix. In a within-subjects design, one treatment was administered to each subject per day on four successive days. The order of treatments was randomized. Subjects rated each treatment on systemic and local effects, and, after the fourth treatment, rank ordered treatments by preference. Results showed little difference between the treatments on local and systemic effects. A majority of patients ranked the addiction specific sites as the most preferred treatment and the helix points as the least preferred. Results suggest that needle insertion into proximate and non-specific sites, common controls in acupuncture research, may be active treatments; power calculations suggest that studies employing these controls will not have adequate statistical power without a very large (>400) number of subjects. Needle insertion into helix regions may be a more suitable needle puncture control.

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THE PRECIPITATION OF COCAINE METABOLITES IN URINE OF ADDICTS UNDERGOING SAUNA BATH TREATMENT

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Recent studies demonstrate that cocaine metabolites may accumulate in the body and that several days to weeks may be required for their elimination. Treatment outcome may be enhanced by methods which accelerate the safe and rapid elimination of drug metabolites. This preliminary study was conducted to determine if a detoxification program utilizing sauna baths as one component may precepitate the presence of cocaine metabolites in urine and sweat. Subjects were Caucasian with ages ranging from 36 to 40 years, and all met DSM-III-R criteria for cocaine dependence and ingested cocaine by the smoking route. Use ranged from 8 months to 18 years, and subjects reported cocaine use on over 75% of days in the month just prior to treatment. Three subjects repotted last use of cocaine within 48 hours of admission, and one subject reported last use 25 days prior to program entry. Between the fifth and eleventh day of residential treatment, and continuing daily for up to five weeks, subjects had multiple sauna baths each day. Urine and sweat samples were collected from subjects every two to three days during this period and tested for cocaine metabolites. Analysis was by polarization fluorescent immunoassay which has a 95% sensitivity of 30 ng/mL. Three of the four subjects showed a measurable increase in sweat or urine cocaine metabolite concentrations when sauna baths were initiated. Two subjects showed undetectable levels of metabolites in urine prior to sauna baths and then demonstrated detectable levels after saunas were initiated. Metabolites were detectable in sweat and urine for up to live weeks following the start of sauna treatment. This study suggests sauna baths and other methods to increase sweating and metabolism may precipitate the appearance of cocaine metabolites in sweat and urine and, thereby, accelerate their elimination from the body.

OXIDE-BRIDGED PHENYLMORPHANS AS OPIOID RECEPTOR PROBES

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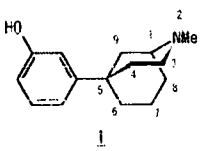
In our continuing study of the opioid receptor system, we have examined conformationally fixed derivatives of the potent class of narcotic agonists, 5-(3-hydroxyphenyl)morphans **1 .** The parent compounds have a rigid 2-azabicyclo[3.3.1]nonane ring system with a freely rotating phenyl group attached at the 5-position. In order to gain an insight into the topological features of opioid receptor binding sites, we have undertaken a study aimed at determining the optimum torsion angle between the phenyl ring and piperidine ring for binding of **1** to an opioid receptor. Our approach is to conformationally restrict rotation of this phenyl ring by means of an oxide bridge to one of three carbons, 4, 6 or 9 of **1.** Each carbon offers two epimeric sites of attachment and the phenyl ring has two regioisomeric positions, therefore a total 12 isomers are possible. We have already reported the synthesis of eight isomers except **2** and **3.** We reported some synthetic approaches to **2.**



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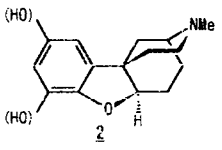

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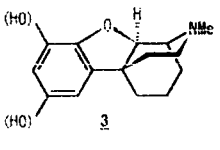

3

FLUORINATED AND IODINATED DERIVATIVES OF THE NONPEPTIDIC DELTA OPIOID RECEPTOR AGONIST SNC 80

S. N. Calderon; H. Kaynkiri; H. Xu; J. S. Partilla, K. M. Becketts; R. B. Rothmam; F. Porreca; and K. C. Rice

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SNC 80 is a nonpeptidic delta (δ) opioid receptor agonist ~2000 fold selective for δ opioid receptors over mu (μ) opioid receptors *in vitro* binding assays and smooth muscle bioassays. Delta opioid receptors have been implicated in mediation of analgesia and in the development of opioid dependence and affective disorders due to the role of endogenous opioid systems in the modulation of the mesolimbic dopaminergic pathway. New, highly potent and selective nonpeptidic δ opioid receptor agonists, antagonists, affinity label and imaging agents are now required to optimally advance the understanding of these effects as well as the development of new medications which act on these sites. Position emission tomography (PET) and single photon emission computed tomography (SPECT) are noninvasive imaging techniques that are applicable to *in vivo* measurement of biochemical function in animals and conscious humans and have provided an invaluable tool in the study of neurotransmitter systems. In such studies, nonpeptidic ligands are advantageous over peptides in that they are generally less subject to metabolism, can penetrate the blood-brain barrier, and therefore can be administrated peripherally *in vivo.* PET studies require the use of positron-emitting isotopes such as ^{11}C and ^{18}F. SPECT techniques are mainly restricted to the use of ^{123}I (photon emitting isotope). In order to gain further insight into the role of the δ opioid receptors *in vivo.* we have designed and synthesized iodinated and fluorinated derivatives of the potent and selective δ opioid agonist SNC 80 as potential PET and SPECT ligands. The work described herein involves the synthesis and biological characterization of the nonradiolabelled targets. Fluorine substitution was introduced by replacement of one of the hydrogens of a methyl of the diethylamide side chain, and iodine substitution was introduced by replacement of the aromatic methoxy substituent. Radioreceptor biuding studies revealed that these two novel ligands retained a high degree of selectivity for δ opioid receptors.

ONE OF THE MOUSE BRAIN DELTA$_{NCX}$ BINDING SITES IS SIMILAR TO THE CLONED OPIOID DELTA RECEPTOR: FURTHER EVIDENCE FOR HETEROGENEITY OF DELTA RECEPTORS

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We recently presented evidence for subtypes of the delta$_{ncx}$ binding site in rat and mouse brain which we termed delta$_{ncx}$] and deltan$_{cx2}$. Cha *et. al.,* (this meeting) report that i.c.v. administration of antisense DNA complementary to the cloned delta opioid receptor (CDOR) to rats decreased [^{3}H]DADL binding to one of the binding sites. Here we compare the binding parameters, ligand selectivity profile and pharmacological properties of the mouse CDOR stably expressed in a cell line to the delta$_{ncx}$ binding sites of mouse brain. [^{3}H]DADL labeled a single binding site in membranes prepared from these cells. BIT-pretreatment had no significant effect on [^{3}H]DADL binding parameters. The DOR had high affinity for delta agonists and antagonists. [^{3}H]DADL labeled two binding sites in mouse brain membranes depleted of mu receptors by pretreatment with BIT: the delta$_{ncx-l}$ site (high affinity for DPDPE and deltorphin) and the delta$_{ncx2}$ site (low affinity for DPDPE and deltorphin). Some agents were moderately selective for the delta$_{ncx2}$ site: [pCI]DPDPE (10.9-fold), JP41 (5.9-fold) and JP45 (3.8-fold). The K_i values of 12 opioids at the mouse CDOR were determined. These values were highly correlated (r = 0.996) with their values at the delta$_{ncx1}$ site but not the delta$_{ncx2}$ site (r = -0.05). These data suggest that the delta$_{ncx2}$ site may be distinct from the cloned delta opioid receptor.

RESOLUTION OF TWO SUBTYPES OF DELTAncx BINDING SITES IN RAT BRAIN USING [^{3}H]DADL: SELECTIVE EFFECTS OF DELTA ANTISENSE DNA

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Quantitative binding studies resolved two high affinity [^{3}H]DADL binding sites in rat brain membranes depleted of mu binding sites by pretreatment with BIT. Assays were conducted in 50 mM Tris-HCl, pH 7.4, containing 100 mM NaCl, 2 μM GTP, 3 mM MnCl2 and 5 mM 2-mercaptoethanol (SS) for 4-6 hours at 25°C. The two binding sites had lower ($delta_{ncx1}$, Ki=96.6 nM) and higher ($delta_{ncx2}$, Ki=1.55 nM) affinity for DPDPE. The ligand-selectivity profile of the $delta_{ncx2}$ site was that of a classic delta binding site. The ligand-selectivity profile of the $delta_{ncx1}$ site was neither mu- or delta-like. The Ki values of selected agents were: ([pCl]DPDPE, 3.91 nM), (DPLPE, 142 nM), (DAMGO, 2.65 nM). Under these assay conditions, [^{3}H]DADL binding to the cells expressing the cloned mu receptor is very low and pretreatment of cell membranes with BIT almost completely inhibits [^{3}H]DAMGO and [^{3}H]DADL binding. i.c.v. administration of antisense DNA to the cloned delta receptor selectively decreased [^{3}H]DADL binding to the $delta_{ncx2}$ site. Viewed collectively, these studies have identified a novel non-mu, delta-like binding site in rat brain.

IDENTIFICATION OF A NOVEL δ OPIOID RECEPTOR BINDING SITE IN RAT BRAIN MEMBRANES

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Our laboratory was among the first to propose the existence of δ receptor subtypes: a δ site thought to be associated with a μ-δ opioid receptor complex termed the δ_{cx} binding site and δ site not associated with the μ-δ opioid receptor complex, termed the δ_{ncx} site. In the present study we investigated, using (+)-trans-SUPERFIT-pretreated membranes, the possibility of heterogeneity of the δ_{cx} binding site. Two sites were resolved: the δ_{cx-1} site at which μ-ligands are potent non-competitive inhibitors and δ-ligands are weak competitive inhibitors and the δ_{cx-2} site where δ-ligands are potent and μ-ligands are weak, mixed competitive-noncompetitive inhibitors. Although the δ_{cx-2} site has δ-like ligand-selectivity profile, several experiments distinguished it from the δ_{ncx} site: 1) administration of δ-antisense DNA to rats selectively decreases δ_{ncx} binding and 2) the δ_{ncx} but not the δ_{cx-2} site is sensitive to (+)-trans-SUPERFIT. Viewed collectively, the major finding of this study is the discovery of a novel SUPERFIT-insensitive and δ-antisense-insensitive δ-like (δ_{cx-2}) binding site.

ENHANCEMENT OF δ-OPIOID RECEPTOR SELECTIVITY OF THE 5-(3-HYDROXYPHENYL)MORPHANS

C. M. Bertha; J. L. Flippen-Anderson; R. B. Rothman; F. Porreca; P. Davis; H. Xu; K. Becketts; X.-Y. Cha, and K. C. Rice

LMC, NIDDK, NIH, Naval Research Laboratory, LCP, NIDA ARC, Department of Pharmacology, University of Arizona Health Science Center

Recent studies have indicated that compounds that bind to the δ-opioid receptor have wide clinical potential. Selective δ-opioid ligands could also be lead compounds for the preparation of affinity ligands and imaging agents, which are used as tools to study the receptors in living animals. As part of our continuing effort towards the development of new δ-opioid ligands, we have synthesized compounds structurally related to the μ-opioid 5-(3-hydroxyphenyl)morphan (1), bearing additional aromatic moieties in that area of three dimensional space necessary for interacting with δ-opioid receptors. Several of these newly synthesized prototypes displayed enhanced affinity and selectivity for the δ-opioid receptor (versus μ) as determined by both *in vitro* binding assays and smooth muscle preparation bioassays. *In vitro* radioreceptor binding studies in rat brain revealed that both of the parent enantiomers, (-)-**1** and **(+)-1,** had a high affinity for the μ opioid receptor (21 nM), a slight affinity for κ_1 opioid receptors (-800 to 900 nM) and even less for the δ opioid receptor (μ/δ IC_{50} ratio of <0.02 for both). A derivative of **(-)-1** containing an indole moiety fused at the C6-C7 position of the phenylmorphan nucleus, (-)-**2,** displayed a >180 fold increase in affinity for the δ opioid receptor with an IC_{50} value of 6 nM. The parent compound **(-)-1** had only 26% agonist activity at 30 μM in the mouse vas deferens (δ) bioassay, whereas compound (-)-**2** had an IC_{50} of 393 nM in this preparation, indicating the importance of the indole moiety in imparting δ-opioid agonist activity to the phenyhnorphan (-)-**1.** A structure-activity relationship (SAR) study of *N*-alkyl derivatives of the racemic nor 2 indicated that they bind in a similar fashion to μ and δ receptors, but not the κ_1 opioid receptor. As studies on the molecular basis of the interaction of opioid ligands with their respective receptors continues to gain momentum, the SAR data described herein for these synthetic phenylmorphans will prove helpful for further studies.

DESIGN OF DYNORPHIN A ANALOGS WITH HIGH POTENCY AND SELECTIVITY FOR κ OR δ OR μ RECEPTORS. IMPLICATIONS FOR OPIOID DRUG DESIGN

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Dynorphin A (Dyn A) binds with subnanomolar potency at the κ receptor, but also has low nanomolar (1-10 nM) binding potency at μ and δ opioid receptors. We have proposed that Dynorphin A (1-11) possesses three structurally distinct regions, the message sequence Tyr^1-Gly^2-G3-Phe^4-Let^5 that targets all three receptors, the selector sequence, Arg^6-Arg^7, that preferentially selects tbe κ receptors, and the potentiator sequence, Ile^8-Arg^9-Pro^{10}-Lys^{11}-NH_2 which increases the potency. To evaluate these concepts we have modified the selector sequence with lipophilic or acidic amino acid residues that favor δ receptors. [$Nle^{67,8}$]Dyn A(1-11)-NH_2 and [$Asp^{6,7}$]Dyn A(1-11)-NH_2 become 10-20 fold selective for δ vs μ receptors and 10-80 fold selective for δ vs κ opioid receptors. Further modification of the message sequence gave analogues that were 80-670 fold selective for δ vs κ and 26-220 fold selective for δ vs μ opioid receptors. Analogues such as [N-Pr-Tyr^1]Dyn A(1-11)-NH_2 and [D- Ala^3]Dyn A(1-11)-NH_2 remain nanomolor binders at κ vs μ (20-350 fold selective) and at κ vs δ opioid receptors (100-1300 fold selective). Some of these analogues also have enhanced stability against proteolytic degradation relative to Dynorphin A.

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IRREVERSIBLE BINDING OF MITPD TO THE CLONED κ OPIOID RECEPTOR AND DETERMINATION OF THE REGION CONFERRING SPECIFICITY

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MITPD, N-*Methyl*-N-[(1S)-1-(4- *i*sothiocyanatophenyl)-2-(1-*p*yrrolidinyl)ethyl-3,4-*d*ichlorophenylacetarnide, is an isothiocyanate derivative of the κ agonist ICI-199,441 (Weerawama *et al.,* J. Med. Chem. 37:2856, 1994), an analog of U50,488H. It has been shown to have high affinity and selectivity to the κ receptor and bind irreversibly to the κ, but not μ or δ, receptor in brain membranes. In this study, we characterized interaction of this compound with cloned μ, δ, and κ opioid receptors and determined the region of the κ receptor that conferred selectivity for MITPD. MITPD inhibited [^{3}H]diprenorphine binding to κ, μ, and δ receptors with IC_{50} values of 0.7 nM, 490 nM and 610 nM, respectively. These results indicate that MITPD has ~ 700- and ~ 870-fold selectivity for κ over μ and δ receptors. Pretreatment with MITPD followed by extensive washing reduced receptor binding with an IC_{50} value of 3.7 nM, but did not affect μ or δ binding at < 1 μM. The reduction in κ binding was due to a decrease in B_{max} with no change in K_d of [^{3}H]diprenorphine. Binding of MITPD to four μ/κ chimeras was examined. Chimera III (amino acid (aa) κ: 1-141/μ151-398) and Chimera lV (aa μ1-150/κ 142-380) were constructed by swapping the regions from the N-terminus to the start of the TMH 3. Chimera XI (aa μl-268/κ263-380) and Chimera XII (aa κ] 1-262/μ269-398) were generated by exchanging the regions from the middle of the third intracellular (i3) loop to the C-terminus. IC_{50} values of MITPD for inhibition of [^{3}H]diprenorphine binding were determined to be 430 nM for III, 1.8 nM for IV, 40 nM for XI and 14 nM for XII. Pretreatment with MITPD followed by extensive washing reduced IV receptor binding with an IC_{50} value of 75 nM, but did not affect III, XI or XII binding at < 1 μM. In summary, MITPD is a highly selective κ irreversible ligand and the region from the third transmembrane helix to the C-terminus of the κ receptor is important for the binding of MITPD.

FLUORESCENT LABELING OF LEUKOCYTE KAPPA OPIOID RECEPTORS USING PHYCOERYTHRIN AND FITC- OR BIOTIN-NALTREXAMINE

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The R1.1 and RIEGO mouse thymoma cell lines express functional *kappa* opioid receptors identical to those expressed in the brain (Lawrence *et al.,* Biochem. Pharmacol. **49:** 81, 1995). Visualization of these receptors by flow cytometry was accomplished by indirect immunofluorescence using the combination of fluorescein-labeled arylacetamide FITC-AA), biotin-conjugated anti-fluorescein IgG, and extravidin-conjugated R-phycoerythrin (Lawrence *et. al.,* PNAS **92:** 1062, 1995). The current study investigated whether a shorter protocol using a biotin-conjugated opioid followed by extravidin-R-phycoerythrin would effectively stain the thymoma *kappa* receptor. FITC-naltrexamine and biotin-naltrexamine bound to the *kappa* receptor in guinea pig brain membranes with high affinity (K_i values of 5 nM and 3 nM, respectively, vs. [^{3}H]U69,593). When fluorescein was measured, PITC-naltrexamine staining of R1EGO cells was not blocked by the *kappa*-selective antagonist nor-binaltorphimine (nor-BNI). However, when R1EGO cells were incubated with 30 μM FITC-naltrexamine followed by biotin-anti-fluorescein IgG and extravidin-R-phycocrythrin, nor-BNI inhibited 36 ± 7 % of the phycoerythrin fluorescence. In contrast, the phycoerythrin fluorescence observed when cells were incubated with biotin-naluexamine followed by extravidin-R-phycoerythrin was not significantly different from the extravidin-R-phycoetythrin background. Thus, the amplification step using biotin-conjugated anti-fluorescein IgG was required to visualize the *kappa* opioid receptor on the R1EGO thymoma cell line. This finding indicates that a three-step indirect immunofluorescence protocol using phycoerythrin optimally stains opioid receptors on cells of the immune system.

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IDENTIFICATION OF SELECTIVE LIGANDS FOR MU, KAPPA AND SIGMA RECEPTORS FROM SYNTHETIC COMBINATORIAL LIBRARIES

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Synthetic combinatorial libraries (SCLs) have been used for the identification of a range of new opioid ligands for the μ opioid receptor. The ligands identified include peptides composed entirely of L- or D-amino acids or composed of a combination of L- and D- amino acids, as well as non-peptidic compounds (polyamines). Both antagonists (the acetalins - *PNAS* 90:10811-10815, 1993) and agonists (all D-amino acid hexapeptides - *Science* 266:2019-2022, 1994) have been identified for the μ receptor using SCLs. Neither the acetalins nor the all D-amino acid peptides bear any obvious sequence relationship to the enkephalins or to other related opioid peptides. In an extension of this work, we have examined four libraries in assays selective for the μ, κ and σ receptors. The four SCLs used were: a) composed entirely of L-amino acids and lacking an N terminal acetyl group; b) composed entirely of D-amino acids and lacking an N terminal acetyl group; c) a chemically transformed L-amino acid SCL in which the amide backbone carbonyls were reduced to methylenes to yield a polyfunctional amine library, and d) a tetrapeptide SCL (nonacetylated) composed of 52 different L-, D-, and unnatural amino acids. The identification process for individual peptide/compounds derived from these libraries will be presented. The relative activities of the most active compounds identified from these libraries will be presented for the μ, δ, and κ receptors. These will be contrasted with the activities of the peptides previously obtained by SCLs and other opioids.

IN VITRO AUTORADIOGRAPHY OF RECEPTOR-ACTIVATED G-PROTEINS WITH AGONIST-STIMULATED [^{35}S]GTPγS BINDING

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Agonists stimulate the binding of [^{35}S]GTPγS to receptor-coupled G-proteins in the presence of excess GDP in isolated membranes. We have developed a novel autoradiographic method which adapts this technique to anatomically identify receptor-activated G-proteins using [^{35}S]GTPγS. We examined stimulation of [^{35}S]GTPγS binding by μ opioid (DAMGO), cannabinoid (WIN 55,212-2) and GABAB (baclofen) agonists. DAMGO stimulated [^{35}S]GTPγS binding in a concentration-dependent manner in both isolated membranes and tissue sections. Maximal DAMGO-stimulated [^{35}S]GTPγS binding was obtained by 3 or 10 μM DAMGO, which produced an approximately 200% increase in thalamic [^{35}S]GTPγS labeling in tissue sections. The receptor specificity of agonist-stimulated [^{35}S]GTPγS binding in brain sections was demonstrated by addition of appropriate antagonists to block labeling. DAMGO-stimulated [^{35}S]GTPγS binding was observed in regions including the striatum, medial thalamus and periaqueductal gray and addition of naloxone completely blocked DAMGO stimulation of [^{35}S]GTPγS labeling. WIN 55,212-2 produced a high level of cannabinoid receptor-stimulated [^{35}S]GTPγS binding in the substantia nigra and globus pallidus, which was completely blocked by SR141716A. The anatomical distribution of receptor-coupled [^{35}S]GTPγS binding was different for each receptor, but in each case corresponded to receptor distributions as determined by receptor binding autoradiography. This technique provides a method of functional neuroanatomy that identifies the activation of G-proteins by specific receptors.

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OPIOID RECEPTOR-MEDIATED STIMULATION OF LOW K_m GTPase IN RAT LOCUS COERULEUS MEMBRANES: EFFECTS OF CHRONIC MORPHINE

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Mu (μ) opioid receptors in rat locus coeruleus (LC) inhibit both adenylyl cyclase and neuronal activity through G-protein-mediated mechanisms. Previous studies have shown adaptive changes in both the cAMP system and ion channel activity in the LC in response to chronic morphine. This study examined the effect of chronic morphine on G-protein activity by measuring low K_m GTPase activity in LC membranes from control and chronic morphine-treated rats. Pharmacological characterization of opioid-stimulated GTPase demonstrated a μ-receptor-mediated response, since the p-selective agonist DAMGO and the non-selective endogenous agonist μ endorphin were both IO-fold more potent than the δ-selective agonist DSLET, the κ-selective agonist U50,488-H produced no effect, and K_e values for naloxone against DAMGO and β-endorphin were 2-5 nM. Chronic morphine treatment did not change the potency or efficacy of DAMGO for stimulation of GTPase in LC membranes. However, the absolute activity of basal and DAMGO-stimulated GTPase was decreased by about 25% in the LC from morphine-treated rats. Kinetic analysis revealed that this change was probably due to a decrease in the V_{max} of the enzyme. To determine whether this change was due to a decrease in GTP hydrolysis per se or due to an actual decrease in G-protein activity, [^{35}S]GTPγS binding studies were conducted in LC membranes. These experiments showed that chronic morphine decreased DAMGO-stimulated [^{35}S]GTPγS binding in the LC similarly to the decease observed in low K_m GTPase. These results suggest that chronic morphine treatment may decrease inhibitory G-protein activity in the rat LC. This decrease may contribute to increased adenylyl cyclase activity through decreased inhibition by G_i, and/or to tolerance to the inhibitory effects of opioids and increased neuronal excitability in the LC through changes in the activity of G_i and/or G_o.

MORPHINE INDUCES FOS EXPRESSION VIA MU RECEPTOR AND PROTEIN KINASE C-ß ACTIVATION: ANTISENSE STUDIES

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Previous studies from this and other laboratories have shown that acute administration of morphine (MOR) regulates immediate-early gene (IEG) expression in rat striatum. We have also shown that acute morphine administration induces translocation of the ßII isoform of protein kinase C (PKC-ßII) in a subset of neurons which also express the IEG c-Fos. In the present work, we tested the hypothesis that inhibition of the m opiate receptor (μOR) or of PKC would block the induction of c-Fos expression in response to acute MOR administration. Two experimental approaches were used, both of which involved the infusion of antagonists via chronic cannulae into specific regions of the brains of male Sprague-Dawley rats. In the first set of experiments, pharmacological antagonists selective for the pOR (ß-flunaluexamine; ß-FNA) or for PKC (chelerythrine; CHEL) were infused acutely into the lateral thalamus (ß-FNA) or the lateral ventricles (CHEL); control animals received infusions of vehicle only. In the second set of experiments, antisense (AS) or missense (MS) oligonucleotides complementary to the mRNA encoding the μOR or PKC-ß were infused into the lateral ventricle, daily for five days. Following the treatment with antagonists, the rats were injected with MOR (10 mg/kg, sc), sacrificed two hours later, and the brains removed for immunocytochemical analysis for c-Fos. Both ß-FNA and μOR-AS inhibited c-Fos expression in dorsomedial striatum, but μOR-MS did not. CHEL and PKC-ß-AS also decreased c-Fos expression in the same brain region. These findings suggest that MOR regulates c-Fos expression in dorsomedial striatum through activation of μOR in thalamus, by a PKC-ß-dependent mechanism, and provides further evidence for a role for PKC in the actions of MOR.

REGULATION OF OPIOID BINDING BY SODIUM IN CELL LINES EXPRESSING TRANSFECTED δ- AND μ- RECEPTORS

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The regulation of the opioid receptor by sodium has been well established for native receptors. The hypothesis that the "sodium shift" predicts agonist activity was tested in cell lines containing individually transfected opioid receptors. Stably transfected CHO cells expressing either the rat δ-opioid receptor or the mouse μ-opioid receptor were used in these studies. These cells show high affinity opioid binding with selectivity for δ- or μ opioids, respectively. We have previously used these cells to evaluate the affinity of a series of (-)-5, 9 α-dimethyl-2-hydroxy-N-substituted-6,7-benzomorpans, The pharmacological activities for these compounds include antinociception, with the (-)-methyl, pentyl, heptyl and hexyl compounds equipotent to morphine in tail flick, phenylquinone and hot plate assays; and narcotic antagonism with the (-)-propyl compound. Competition assays were performed with this series of compounds in the presence and absence of 150 mM NaCl using [^{3}H]diprenorphine to measure opioid receptors in P_2 membrane preparations. Agonist binding was reduced 5-50 fold in the presence of sodium, whereas antagonist binding was only slightly altered. These studies demonstrate that cell lines expressing the cloned μ and δ-opioid receptors show appropriate regulation and can serve as model systems for determining the binding properties of opioid ligands.

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AUTORADIOGRAPHIC AND BEHAVIORAL EVIDENCE OF μ-OPIOID RECEPTOR OVEREXPRESSION IN TRANSGENIC MOUSE BRAIN

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Efforts to increase μ-opioid receptors in the mouse brain were approached using 4.8 kb rat tyrosine hydroxylase promoter linked to 2.2 kb rat μ-opioid receptor cDNA. This fragment of the TH promoter has been shown to drive reporter gene expression in catecholaminergic neurons. Therefore, to characterize potential transgene overexpression, in vitro receptor autoradiographic distribution of the selective μ ligand, ^{125}I-DAMGO, was determined in brain sections of these transgenics (THM4) and their nonuansgenic littermates (n = 6, each group). In brain regions normally expressing μ receptors, ^{125}I-DAMGO binding increased 30-36% in the THM4 compared with the wild type littermates. The regions include the medical prefrontal cortex, the anterior caudate putamen, and the shell of the nucleus accumbens. Analgesia studies were conducted comparing THM3 (n = 5) and THM4 (n = 12) to nontransgenic wild type littermates (n = 5 and 12, respectively). A parallel leftward shift in the morphine dose-dependent curve was found in the transgenic strains for the hotplate test (supraspinal action) but not for the warm water tail-flick test (spinal action). Preliminary studies showed that, 72 hours after s.c. morphine-pellet (6.57 mg) implantation, the nontransgenic strain displayed more naloxone-precipitated withdrawal signs than the THM4. This transgenic strain provides an animal model for studying the effects of altering the expression of a single gene (the μ opioid receptor) on sensitivity to opiate drugs of abuse.

QUANTITATION OF PREPRODYNORPHIN mRNA IN GUINEA PIG BRAIN BY TCA PRECIPITATION OF mRNA-cRNA HYBRIDS

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For some aspects of the endogenous opioid system the guinea pig may prove to be a good model for studies of the human opioid system. To measure levels of guinea pig preprody-norphin (ppDYN) mRNA by solution hybridization using a species-specific probe, we have cloned and sequenced a fragment of the guinea pig ppDYN gene containing the entire coding region for the prepropeptide. A 1140 bp fragment of the gene was subcloned to serve as a template for synthesis of ^{32}P-cRNA as a hybridization probe. For quantitation of ppDYN mRNA in selected brain regions of guinea pigs, we used a solution hybridization RNase protection TCA precipitation assay. The densities of the ppDYN mRNA (pg per µg of total RNA, ±SEM) in brain regions were as follows: olfactory nucleus-0.90± 0.06, frontal cortex- 1.35± 0.09, nucleus accumbens- 4.47±0.29, caudate putamen-2.17±0.31, hippocampus-1.69±0.13, hypothalamus-1.64±0.27, amygdala- 2.54±0.54, cerebellum-0.26±0.09, pons/medulla- 0.46±0.03. Comparison of ppDYN mRNA levels in the guinea pig with our previous determininations in rat brain showed that both species had similar content of mRNA in nucleus accumbens, caudate putamen and hypothalamus. However, whereas ppDYN mRNA was not detected in olfactory nucleus, pons and cerebellum of the rat, there was significant mRNA density in these regions of the guinea pig brain.

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HIBERNATION-RELATED REGIONAL CHANGES IN BRAIN MU, DELTA, AND KAPPA OPIOID RECEPTOR BINDING

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The development of morphine dependence is greatly reduced in the hibernating (H) state of the ground squirrel (*Citellus lateralis*). This study tested the hypothesis that the suppression of dependence is due to a general reduction in opioid receptor binding. *C. lateralis* were sacrificed in the non-hibernating (NH) and H states and their brains prepared for autoradiography of µ ∂, and κ l binding. µ-Opioid binding sites were labelled with 1.0 nM [^{3}H]DAGOL. ∂-(Opioid sites were labelled with 2.0 nM [^{3}H]DADLE in the presence of 300 nM [D-pro^4]morphiceptin, to suppress interaction with it sites. κ-(Opioid binding sites were labelled with 1.0 nM [^{3}H]diprenorphine in the presence of 300 nM [D-pro^4]morphiceptin and 100 nM DSLET, to suppress interaction with µ and ∂ binding sites, respectively. To defuse [^{3}H]diprenorphine binding to κ_1 sites, adjacent sections were co-incubated with 200 nM U-50,488H. Nonspecific binding of each radioligand was defined by co-incubating adjacent sections with 1 µM naloxone. The data displayed an overall trend of decreased µ binding in the H state in cortex, basal ganglia, and hippocampus. In contrast, a trend of increased µ binding in the H state was evident in limbic system areas (nuc. accumbens, hypothalamus, periaqueductal gray, and olfactory tubercle). ∂-lReceptor binding was similar across the two states. A trend of increased κ_1 binding in the H state was evident in caudate nuc., globus pallidus, nuc. accumbens, lateral septum, ventromedial hypothalamus, and arcuate nuc. Our results show that whereas the reduction of morphine dependence in the H state is not due to a general decrease in opioid receptor binding, it may reflect regional changes in the relative binding of µ, ∂, and κ_1 receptors. Moreover, the increase in µ and κ_1 binding in limbic system areas supports the notion that opioid peptide systems participate in the control of the H state.

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COST-EFFECTIVENESS OF CONTINGENCY CONTRACTING WITH OPIOID ADDICTS IN METHADONE TREATMENT

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Opioid addicts participated in a six month methadone detoxification study comparing the effectiveness of intensive psychosocial treatment with or without contingency contracting for drug-free urines. Fifty-one subjects were randomly assigned to each condition. Rewards could be obtained during the first 120 days of treatment by proving urines free from all drugs. Due in large part to the substantial number of subjects in the contingency condition earning minimal or no rewards, the two groups did not differ in average per-subject cost: $3,898.41 for the Contingency Group and $3,698.39 for the Non-Contingency Group ($t_{(100)}$=.70, p<.48). Over the 120-day period, subjects in the Contingency Group produced an average of 26.2% drug-free urines, while the Non-Contingency Group produced 17.0% (a nonsignificant difference). Cost-effectiveness analyses showed that each percentage point improvement in outcome could be obtained by an average incremental treatment cost of $22. An average incremental treatment cost of $146 per contingency subject was associated with an additional ten percentage points of the subjects providing completely clean urines during the last month of treatment.

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AN EVALUATION OF THREE CONTINGENCY MANAGEMENT PROTOCOLS IN A METHADONE MAINTENANCE PROGRAM

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This study examined the effects of using vouchers to reinforce either the provision of urines testing free of unauthorized substances (UA group) or the completion of objectively defined treatment plan-related tasks (TP group). Vouchers could be exchanged for cash - as long as the patients used the money to achieve treatment plan goals while also providing documentation - *e.g.,* receipts. A third group was assigned to the clinic's standard treatment protocol which included loosely defined contingencies in the form of privilege "levels" for subjects demonstrating extended periods of abstinence (STD group). Subjects were randomly assigned to UA, TP, or STD condition after a six week baseline period. In the UA condition, subjects earned ten vouchers for each urine testing free of unauthorized substances (x3 weekly testing; EMIT). In the TP condition, subjects earned up to 30 vouchers a week if they demonstrated completion of objectively defined tasks that were collaboratively devised with their counselors on a weekly basis and that related to long-term treatment goals. Contingencies were in effect for all groups for a total of twelve weeks. A total of $\underline{N}$ = 104 subjects was recruited, including n = 41 TP subjects, $\underline{n}$ = 28 UA subjects, and $\underline{n}$ = 35 STD subjects. Abstinence from all illicit drugs was the main dependent measure. Repeated-measures ANOVA (n=104) indicate a significant main effect on abstinence for time in treatment ($\underline{F}$ (2, 202) = 3.95, $\underline{p}$ < .05), and a significant group X time interaction (F = 5.30; df = 4,198; p<.01). Post-hoc analyses indicate that the main effect for time is largely accounted for by a significant increase in abstinence rates within the TP group; no significant increases in abstinence rates were observed in either the UA or STD subjects over time. The results suggest that the reinforcement of clearly defined behavioral tasks that are targeted toward long-term goals increases involvement in behaviors inconsistent with drug use behavior among methadone maintenance patients. Further, TP addresses a broad range of problem areas, is highly effective in reducing drug use, and seems particularly effective in improving attitudes toward and compliance with treatment.

CONTINGENCY CONTRACTING FOR ILLICIT DRUG USE WITH OPIOID ADDICTS IN METHADONE TREATMENT

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The study examines the effect of positive contingencies in the treatment of heroin addiction. Data are presented on 102 subjects admitted into a six-month methadone treatment which provided for 80 mg methadone per day, an enhanced psychosocial treatment Urine samples were collected at random twice a week and analyzed for opioids, cocaine, benzodiazepines, marijuana, amphetamine, and barbiturates. Subjects were randomly assigned to a contingency or non-contingency contract condition during the first four months of treatment. Subjects in the contingency condition were able to earn increasing cash credits (up to a maximum of $755) to be spent on items of their choice for submitting urine samples demonstrating consistent avoidance of illicit drug use. There were no differences between the two groups demographically, in methadone dose, retention, or psychosocial treatment received. By the last month of the contracting period, the subjects in the contingency group submitted significantly more consecutively clean urine tests (2.9) compared to the non-contingency group (1.1)--p<.0069, as well as more "clean" tests (34% versus 17%)--p<.0345. We conclude from these results that contingency contracting may be a useful adjunct to treatment of heroin addicts who are also poly-substance abusers.

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BEHAVIORALLY CONTINGENT PHARMACOTHERAPY FOR OPIOID ABUSERS: AN OUTPATIENT RANDOMIZED CLINICAL TRIAL

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The present six month clinical trial evaluated the effectiveness of a new treatment model that fully integrates pharmacological treatment (*i.e.,* methadone) with psychosocial treatment (*i.e.,* counseling). Forty opioid abusers participating in methadone substitution therapy were stratified on baseline cocaine use and antisocial personality disorder and randomly assigned to the Experimental (n = 19) or Control (n = 21) group. Patients in both groups were referred for increased intensity of weekly counseling based on rates of drug **use** and counseling attendance. The highest level of counseling consists of approximately nine hours of weekly counseling (individual, group, and significant other). Patients in the Experimental group were informed that continuation of methadone substitution was contingent on attending all weekly counseling sessions. Control group patients were told that continued methadone substitution was independent of counseling compliance. Data is presented for the first 90 days of treatment. Both groups received similar doses of methadone (Exp = 55 mg; Con = 58 mg, NS) and exhibited similar rates of attrition (Exp = 5% drop-out; Con = 14% drop-out, NS). Experimental patients were much more likely to comply with psychosocial treatments (Exp = 80%; Con = 27%; $\underline{p} < .05$) and to bring drug-abstinent significant others into treatment (Exp = 83%; Con = 0%, $\underline{p} < .05$). Further, Experimental patients submitted significantly fewer opiate-positive (16% vs. 45%; $\underline{p} < .05$) and cocaine-positive (27% vs. 50%, $c < .05$) urines than Control patients. Preliminary results support using behavioral contingent pharmacotherapy in opioid substitution programs.

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MEDICAL STATUS AND RESPONSE TO BEHAVIORAL TREATMENT IN METHADONE MAINTENANCE

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Preexisting medical conditions (past history of trauma or head injury, seizures, abnormal liver enzymes, positive skin test for tuberculosis, HIV seropositivily, current alcohol abuse) may be associated with poor response rate to traditional drug abuse treatment. Behavioral contingency management (CM) has been shown to improve rate of sustained abstinence in methadone patients who continue to use illegal drugs. We compared the medical data of patients responding (≥ 5 weeks negative urines) or not-responding to either form of treatment. Methadone maintained patients were allocated either to a CM group (n = 53), receiving vouchers exchangeable for goods and services for providing cocaine or opiate free urines, or to a control (NCM) group (n = 35). Medical data were obtained through chart review. Data from 88 patients are presented (males 67%, African-American 52%, mean age 39 ± 0.6 years). The rate of preexisting medical conditions was 82%: past history of (h/o) trauma 30%; h/o head trauma 19%, h/o seizures 8%, elevated liver enzymes 38%; HIV seropositivity 8% (13% refused HIV testing), current alcohol abuse 26%. The rate of responders was 47% and 26% in CM and NCM group respectively; the presence or number of preexisting medical condition(s) did not predict treatment outcome in either group by Chi-square or by ANOVA. This suggests that in patients participating in drug abuse treatment research, preexisting medical complications do not influence treatment outcome. It is possible that these finding are limited due to the selection process of research participants. In spite of this selection process however, more than 80% participant to drug abuse treatment research have a preexisting medical condition.

NEUROPSYCHOLOGICAL (NP) EXAMINATION OF METHADONE-MAINTAINED (MM) PATIENTS

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Preliminary results of an ongoing longitudinal study of the relationship among NP test outcomes, affective factors and methadone dose in MM former heroin addicts indicate significant variability in subjects' performances on sensitive measures of attention, memory, language, mental flexibility and perceptual-motor functioning. Consecutive outpatient clinic referrals for the first 35 subjects yielded 29 completed lest batteries. This sample included 12 women and 17 men (age = 34.2± 8.6 years; education = 11.8 ± 2.6 years), largely unemployed (76%), predominantly right-handed (76%). receiving daily methadone (dose = 72.1 ± 24.7 mg; range = 15-100 mg) for a minimum of 45 days at initial evaluation. Mean lest performances on measures of sustained attention, naming abilities, verbal and visual memory, fine motor dexterity and speed rated as borderline-mildly impaired relative 10 normative samples, with all subjects deficient on three or more measures. Pearson correlation coefficients indicated that test results were not related lo emotional distress, duration of methadone use or dose. Salient premorbid factors (*e.g.,* history of head trauma, physical abuse, learning disability) failed to classify MM subgroups with identified NP impairment. Annual re-evaluation of seven subjects to date found NP functioning to be consistent over lime. Further investigation of particular (poly)drug abuse histories, concurrent drug use and agents used may help to clarify impairments detected and identify those who may be better candidates for psychosocial and vocational rehabilitation.

ACKNOWLEDGEMENTS:

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USE OF THE SF-36 TO MONITOR IMPROVEMEN'tS IN THE HEALTH OF METHADONE MAINTENANCE PARTICIPANTS

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The SF-36 is a general health survey comprising of 36 items which yield values on eight subscales: (respondentís perception of) general health, mental health, pain, physical functioning, social functioning, role functioning-physical, role functioning-emotional, vitality. The SF-36 was administered to a group of 150 heroin users, consecutive entrants to a public methadone maintenance program. The results were compared to the general population and two clinical groups: patients with major medical and with psychiatric problems. The results showed that heroin users at entry to methadone maintenance had significantly worse physical and psychological health than the general population. Scores were lowest on the general health scale, the social functioning scale and the scales related to impairment of daily functioning. In comparison with other clinical groups, their scores were most similar to the psychiatric patients, although their perception of general health was worse than this comparison group.

Fifty-two clients who remained lo the methadone program for a period of twelve months were assessed on two further occasions, once during the first six month period and once during the second. The result showed significant improvements in five of the eight scales (physical functioning, social functioning, role-physical, role-emotional and mental health), with most of the change occurring within the first six months. At follow-up the greatest differences from the general population were in subjectsí perception of their own health, social functioning and pain. The improvement in health status was associated with a decline in use of medical services. The SF-36 appears to be a sensitive instrument for detection of changes in health status of methadone maintenance participants.

DAY HOSPITAL VERSUS INTENSIVE OUTPATIENT TREATMENT IN AN HMO: DURING TREATMENT MEASURES AT EIGHT WEEKS

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This paper presents eight week follow-up results of random assignment of the first 300 study patients to two treatments, each eight weeks in duration: 1) Day hospital (42 hours/week for three weeks and then six hours/week during the next five weeks. 2) Intensive outpatient (4-1/2 hours/week for eight weeks). Both are followed with ten months similar aftercare. The treatment site is a large staff model HMO's substance abuse program. Demographic Characteristics include women 33%, African Americans 13% Hispanics 14%. Most common substance disorders include amphetamine, marijuana, cocaine, and alcohol dependence. Analysis of the first 300 study subjects found that day hospital and outpatient have similar retention rates at eight weeks. Bivariate analysis found most change in measures of substance use and social functioning (medical, employment, legal, framily/social problems at admission) were similar for both programs at eight weeks. Logistic regression analysis, controlling for socio-demographic characteristics, ASI composite scores, and amount of pressure to enter treatment, did not find type of treatment to predict treatment completion (p=.14). In other logistic regression analysis controlling for the same measures, subjects randomized to the day hospital program were more likely to be abstinent from all substances (p=.04, OR=1.88) at eight weeks than those randomized to outpatient.

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FAMILY MANAGEMENT, BONDING, AND CHILD OUTCOMES IN FAMILIES WITH OPIATE DEPENDENT PARENTS

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Little research has been done on preventing drug use and other problem behaviors among children of drug abusers. This poster presents dam from Focus on Families (FOF). an experimental evaluation of an intervention with families headed by parents receiving methadone treatment. The FOF intervention attempted to help substance abusers avoid relapse, provide better family management, and increase family bonding. Preliminary analyses have shown that the intervention increased parents' skills and sense of self-efficacy in high-risk situations and reduced their drug use. The analyses, however, did not demonstrate robust direct effects on the children. In this poster we present a test of the model underlying the intervention. Using data on subjects in both the experimental and control groups, we examine the effects of parent drug use, family management, and family bonding on child outcomes. We present analyses of direct effects and the interaction between parent drug use and family bonding. The interaction effects illustrate that continued parent drug use moderates the impact of family bonding on child outcomes. The results reinforce the strategy underlying the FOF intervention. Specifically, the results suggest the importance of programs to reduce relapse among drug addicted parents. Once abstinence is maintained parenting skills programs may improve child outcomes.

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STAGE OF CHANGE PROFILES IN PRIMARY OPIOID ADDICTS ABUSING MULTIPLE SUBSTANCES

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Investigated intake "stage of change" profiles in 102 polysubstance-abusing primary opioid addicts in a research-based 180-day methadone program. Examine relationships between emerging stage profiles and markers of treatment readiness. Based on University of Rhode Island Change Assessment (URICA) scores, four stage profiles from other's earlier work were replicated: Precontemplation (PC) (n = 18), Uninvolved (U) (n = 42), Contemplation (C) (n = 23), and Participation (PA) (n = 19). Subjecls were an average age of 40.5 years, primarily White (39%) and African American (34%), male (71%), unemployed (74%), single (40%), living in a house or apartment (89%), and without pressing legal issues (75%). Intake stage was unrelated to those demographic variables; however, based on Wilcoxon rank scores, PA individuals had more education (12.3 years) than U (11.9), C(11), and PC (10.9) individuals ($p < .004$). On "desire to quit", PA and C individuals (8.9, 8.8) reported greater desire than PC and U individuals (both 7.8) ($p < .004$), while on "expectations of success", PA individuals had the highest expectations (8.6), followed by those in C (8.2), PC (7.5), and U (7.1) ($p < .003$). PA individuals (89.5%) were also more likely to report a treatment goal of "quitting opioid use completely", as compared to C (65.2%). PC (55.6%), and U (33.3%) individuals ($p < .001$). We conclude that URICA profiles are useful for understanding treatment readiness in this population. Methods of assessing stage-related cognitive variables in this population, however, warrant continued investigation.

STAGES AND PROCESSES OF CHANGE AS PREDICTORS OF DRUG USE IN METHADONE MAINTENANCE PATIENTS

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This study assesses the validity and clinical utility of Prochaska and DiClemente's stages-of-change model in a methadone maintenance treatment setting by using it to predict short-term abstinence in a sample of 82 newly admitted patients. The model postulates that behavior change occurs in relatively discrete stages -- each stage characterized by particular attitudes and intentions and by the use of different change processes. In the present study, we used previously validated stage and process measures administered one month after admission to predict thrice-weekly urinalysis results collected over a 12-week follow-up period.

Baseline and follow-up abstinence rates were measured by the number of urine specimens testing negative for unauthorized substances (clean urines) provided during a four week pre-test period and a 12-week post-test period. Follow-up abstinence rates differed significantly across stage categories with subjects in Precontemplation and Contemplation stages providing less than 2% clean urines during the follow-up period. A hierarchical regression analysis indicated that, as a group, dimensional stage and process measures significantly improved prediction of follow-up abstinence beyond that afforded by baseline clean urine rates, though only two of the eight measures contributed significantly in the equation.

The results provide equivocal support for the generalizability of the model and highlight some of the difficulties in implementing effective methadone maintenance treatment.

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PREDICTORS OF HEROIN, COCAINE, AND MARIJUANA USE IN FOUR METHADONE MAINTENANCE TREATMENT PROGRAMS

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This study investigated predictors of heroin, cocaine, and marijuana use during early methadone maintenance treatment (MMT). Predictors were from four domains: demographic characteristics, recent use of other drugs, health variables, and treatment variables. Subjects were 154 male and female patients from four MMT programs in the San Francisco Bay Area. Median treatment duration was six months. After a two week induction (Prestudy), subjects were assessed twice per week for up to eight weeks (Study). At all assessments, subjects completed interviews and questionnaires and provided urine samples. Results showed that illicit drug use was highly prevalent. In the eight week Study, the heroin metabolite morphine was detected at least once in 64.3% of the sample, benzoylecgonine in 57.1%, and THC in 40.3%. Site differences were found for heroin and cocaine use. Numerous demographic characteristics and Prestudy use of other drugs (including benzodiazepines and nicotine) predicted illicit drug use during the Study. Further, in multiple logistic regressions with site controlled, demographic variables and Prestudy use of other drugs contributed independently to explaining drug use. Significant ($p<.05$) independent predictors of heroin use were being unmarried and Prestudy marijuana use. Cocaine was positively associated with African-American ethnicity, age, lack of full-time employment, illegal income, problematic legal status, attending church, and Prestudy heroin use. Marijuana predictors were male gender, African-American or Caucasian ethnicity, and Prestudy cocaine use. In view of the cross-predictiveness of drugs, MMT programs may need to target each drug individually to help patients achieve treatment goals.

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PREDICTORS OF TREATMENT RETENTION OF OPIATE DEPENDENT PATIENTS IN OUTPATIENT TREATMENT PROGRAMS

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Outcome studies in opiate and cocaine dependent patients have suggested that an early dropout from treatment is associated with more severe premorbid clinical, social and psychopathological characteristics. Using data from a six month follow-up interview, we conducted a comparative study between 38 opiate dependent patients who stayed in treatment for six months and a selection of 38 opiate dependent patients (matched by gender and age) who dropped out early. All of the patients were attending outpatient clinics in the Valencian Community (Spain). When entering treatment all the patients provided a clinical history which included information on clinical, toxicological, social and criminal variables. In addition, the Symptom Checklist-90, the Beck Depression Inventory and the State-Trait Anxiety Inventory were also administered. Statistical analysis was performed using the X^2 test for categorical data, Fisher's exact test was employed when sample size was insufficient to calculate X^2. No statistically significant differences were found between the two study groups. Thus, none of the variables evaluated in the present study were predictive of treatment retention among our sample. Additional studies are needed to further evaluate other variables such as treatment modality or family structure, that might be of crucial importance in predicting early dropouts or retention of drug dependent patients in treatment programs.

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ESTIMATED VERBAL INTELLIGENCE AS A PREDICTOR OF ATTRITION IN METHADONE SUBSTITUTION THERAPY

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Previous research with alcohol and drug abusing populations has shown relationships between intellectual functioning and treatment retention. The present study extends this research to a population of 370 opioid dependent individuals admitted to an outpatient methadone substitution therapy program. They had a mean age of 35 years, 48% were female, and 61% were white. Patients were administered the Quick Test for Intellectual Functioning (QT). The QT is a perceptual-verbal measure of intellectual functioning that can be administered in less than 10 minutes, producing scores that correlate highly with the WAIS. The average QT score of this sample was 87.80 (S.D.=8.07). The average 12-month retention rate in the program was 212.16 days (S.D.=125.22). Using a Pearson product-moment correlation, no significant relationship was found between estimated verbal intelligence and retention in methadone substitution treatment. It should be noted that the overall low scores observed on the IQ measure may reflect a truncated distribution and may therefore have limited value as a predictor of treatment retention. Treatment retention did, however, show small but significant ($r<.15$), positive correlations with age, being employed at admission, and having a later age at onset of opioid use.

PREDICTING WHICH PATIENTS DO WELL ON METHADONE MAINTENANCE

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This is an initial research report of an ongoing prospective study of opioid dependent patients in a French methadone maintenance program (MMP). The data presented was gathered from the first 29 patients enrolled in the MMP. The two **objectives** of this preliminary analysis are to determine: 1) the extent of overall improvement after three months of treatment (T3) at the MPP and 2) if there are clinical predictors, at baseline (TO) of persistent opioid use at T3. All subjects met DSM-III-R criteria (using the SCID short version) for opioid dependence. **Method:** At T0 and T3, each subject had a psychiatric interview and a physical examination and was administered the Addiction Severity Index (ASI), the Beck Depression and Spielberger Anxiety Inventories (BDI, STAI), the Way of Coping Check List (WCCL) and the Notthingham Health Profile (NHP)]. Urine specimens were analyzed for substances of abuse at baseline and weekly throughout the study **Analysis and Results:** A preliminary analysis of the first 25 subjects, treated with an average daily methadone dose of 85 mg, who reached T3 revealed: 1) significanl improvement between T0 and T3 in substance use (65% of clean urines), anxiety, depression, legal and physical stale (Student t test, $p < 0.05$), and 2) that, in a stepwise discriminant analysis (with four variables) used as an exploratory tool, BDI and WCCL (emotion focused coping) classified correctly 68.08 % of the subjects in either the opiate user or the abstinent group. If the very small size of the sample did not bring some limitations, these results could have confirmed the prevailing role of the psychopathology among the predictors of the opiate use outcome. **Conclusion:** The results of this preliminary analysis indicate a dramatic decrease in opiate use and an improvement in psychiatric, legal and health state after three months of treatment. A discriminant analysis, used as an exploratory tool, needs to be confirmed with a larger sample. This longitudinal study is still active and full results will be reported later.

COMMUNITY REINFORCEMENT APPROACH AND RELAPSE PREVENTION IN THE TREATMENT OF OPIOID DEPENDENCY

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We examined the effectiveness of the Community Reinforcement Approach (CRA) alone and in combination with Relapse Prevention (RP) as compared to Standard (S) drug counseling in opioid addicts on methadone maintenance. Our hypothesis was that CRA would do better than Standard drug counseling and that RP would have an additive effect. There were 180 subjects randomized into three groups: S, CRA, and CRA/RP. Of these, 151 subjects were engaged in treatment and followed-up at six months. Heroin use, relapse to heroin use, and other outcome variables were measured including the Addiction Severity Index (ASI), Beck Depression Index (BDI), Symptom Checklist-90 (SCL-90), Weissman Social Adjustment Scale (SAS-SR), and Risk Assessment Battery (RAB). There were significanl differences found in heroin use, relapse to heroin, $\underline{d}(1) = 5.265$, $p = .022$, and the ASI drug composite scores, $F(1, 148) = 4.37$, $p = .038$, the CRA groups doing better than the S group. At six months all groups showed significant improvements in most variables measured. No between group differences were found on the BDI, SAS-SR, SCL-90, and the RAB. These results suggest that heroin dependent individuals who are stabilized on methadone, may benefit from the addition of CRA/RP procedures.

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PROXIMITY TO OUTPATIENT ADDICTION TREATMENT CENTER AND RETENTION RATE

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Rates of attrition at outpatient drug treatment programs are typically high. It was hypothesized that a subject's traveling distance to the treatment selling may impact retention. Two hundred and twenty-five opiate addicts participating in a double-blind comparison study of methadone vs. buprenorphine maintenance comprised the sample. Subject's daily traveling distance was measured from the treatment center to the central point of the residential zip code. Length of stay was measured from first to last dose of study medication. Correlation analysis indicated that distance is a poor correlate of retention (r=-.0159). Regression analysis found that group and year's of addiction resulted in a multiple r=.30, significance of F=.0004. The data suggest that clinic proximity and medication are secondary to length of opiate abuse history in predicting treatment retention.

INTERVENTION WITH DISCHARGED METHADONE PATIENTS: A HARM REDUCTION APPROACH TO METHADONE AFTERCARE

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Heroin dependence is a chronic relapsing illness. Approximately 70% of all discharged methadone patients relapse and meet dependence criteria within a year. In view of these relatively high rates of recurrence, we conducted a study 10 evaluate the efficacy of a standardized intervention to engage discharged methadone patients into appropriate treatment services. All methadone clients discharged from the PVAMC clinic over a six month period were randomized to an experimental (N=65) or control (N=45) condition at a 2:1 ratio. Overall, 94 patients (85%) were located within a four week window of their one year discharge date, however; nine (10%) were deceased. After informed consent, all subjects completed the follow-up version of the Addiction Severity Index and the Risk Assessment Battery. Additionally, subjects in the experimental group met with a social worker to discuss current treatment needs and were referred, if necessary, lo appropriate services. Telephone contact was provided over a four week period to support subject participation in these services. Results indicate 91.8% (78/85) of the subjects had used opiates in the past month and 82.4% (70/85) were opiate dependent. Of the 51 subjects contacted in the experimental group, 21 were currently enrolled in treatment. Of the 30 subjects not enrolled in drug treatment two reported no current problems, one was incarcerated, and 27 subjects reported problems with drug use in the past 30 days Afler the intervention, 17 of these 27 subjects entered drug treatment. Thus, the intervention was effective in 63% of the cases. Of the 34 subjects contacted in the control condition, 16 were currently enrolled in treatment, two were incarcerated, two reported no current drug use and, 14 reported current drug problems. However, only 1 of these 14 subjects entered drug treatment during the four week observation window. Although still preliminary, this study has public health implications and suggests that an aftercare inrervention provided to discharged methadone patients may engage intravenous drug users 10 participate in appropriate treatment services, thus reducing high risk behaviors.

TAKE-HOME DOSES AS REINFORCERS OF ABSTINENCE FOR METHADONE MAINTENANCE PATIENTS

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Weekly urine toxicology profiles of methadone patients (n=96) were examined for 16 weeks before and 16 weeks after institution of a policy which provided take-home doses of methadone for submission of negative urine specimens. Prior to implementation of the policy, except for Sunday take-homes given to all patients, take-homes could be earned only by patients who had methadone doses 60 mg or less, submitted at least four consecutive weeks of negative urine specimens, and documented outside constructive activities. After the policy change patients could earn take-homes regardless of dose level or outside activity by submitting negative specimens. For each two consecutive weeks of negatives, patients could earn one extra ongoing take-home per week to a maximum of four after six weeks but would lose one ongoing take-home per week for any positive specimen. Thus, continual reinforcement for abstinence and punishment for drug use occurred. For subjects who could be expected to improve (*i.e.* those positive during the baseline period, n=54, 56.3%) percentage of total positive urines declined from the baseline (mean=22.6%, SD=20.3) to the experimental period (mean=17.0%, SD=19.9; $p<.008$. Wilcoxon signed ranks test). A significant change occurred also for the total sample from baseline (mean=12.7%, SD=18.9) to experimental period (mean=10.3%, SD=17.0; $p<.05$, Wilcoxon). These results validate findings of earlier research that take-home doses serve as effective reinforcers of abstinence among methadone patients.

BUPRENORPHINE'S EFFECTS ON "SPEEDBALL" COMBINATIONS OF COCAINE AND HEROIN

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Buprenorphine, an opioid mixed agonist-antagonist, significantly reduced both cocaine and opiate self-administration by rhesus monkeys and human polydrug abusers. We have developed a primate model of *"speedball"* self-administration involving the simultaneous injection of intravenous cocaine and heroin. This study examines the effects of buprenorphine (0.0075-0.75 mg/kg) on self-administration of different heroin and cocaine combinations that maintained the highest rates of responding. Each buprenorphine dose was studied for ten days and presented in an irregular order. Drugs and food (1 gm banana pellets) were available in four daily sessions on a second-order (FR4 VR16:S) schedule of reinforcement. Buprenorphine (0.075-0.75 mg/kg/day) selectively reduced self--administration of speedball combinations of 0.001 mg/kg/inj cocaine and 0.001 or 0.003 mg/kg/inj heroin ($p < 0.05$-0.01). Buprenorphine (0.237 mg/kg/day) shifted the ascending limb of the dose-response curve for speedball combinations of 0.001 mg/kg/inj cocaine and 0.001-0.032 mg/kg/inj heroin downwards and approximately 1 log unit to the right with minimal effects on food-maintained responding. These findings suggest that buprenorphine reduced the reinforcing effects of speedball combinations over this dose range. However buprenorphine treatment (0.075-0.75 mg/kg/day) had minimal and inconsistent effects on speedball combinations of a higher dose of cocaine (0.01 mg/kg/inj) and low or intermediate doses of heroin (0.0001 and 0.001 mg/kg/inj). These studies are still in progress. These data attest to the feasibility of maintaining speedball self-administration in rhesus monkeys and using this model to evaluate the effects of potential treatment medications.

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INTER-REINFORCER INTERVAL AS A MEASURE OF DRUG REWARD

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The breakpoint in progressive ratio (PR) is believed to reflect reinforcing value between doses of a self-administered drug. Direct comparisons, however, between cocaine and heroin has been precluded because different PR schedules have been used. In a previous study, self-administered cocaine (150, 300 and 600 µg/kg/inj), heroin (9, 18 and 36 µg/kg/inj) and the combination ("speedball") (150C/BH, 300C/18H and 600C/36H) were compared under identical schedules. Within this narrow dose range, breakpoints for cocaine and heroin increased as a result of dose, while breakpoints for the combination did not differ between doses. The breakpoint for cocaine was greater for cocaine than for heroin, or the combination. Analysis of inter-reinforcement interval (IRI) and session duration, however, revealed significant differences in IRI and session duration as a result of dose in all drug groups. This data suggests the IRI and session duration may be more sensitive measures of changes in reward valence than breakpoints and could serve as a method of comparing relative reinforcing value of different drug treatments.

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SELF-ADMINISTRATION OF COCAINE AND HEROIN COMBINATIONS UNDER A PROGRESSIVE-RATIO SCHEDULE IN RHESUS MONKEYS

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Four rhesus monkeys prepared with chronic intravenous catheters were trained to lever press for cocaine (C) injections under a progressive-ratio (PR) schedule of reinforcement. The PR schedule had five components, each with four trials with the same response requirement (*i.e.,* 20 trials total). The response requirements were fixed ratio (FR): 120, 240, 480, 960, 1920. Trials were separated by an intertrial interval (30 mm) and each trial ended with an injection or expiration of a limited hold (15 min). A session ended when the FR was not completed within the limited hold for two consecutive trials. When responding maintained by C (0.1 mg/kg/inj) was stable (± 10% variation in mean inj/session for three consecutive sessions), saline (S) was substituted for C until responding was at low levels and stable. Responding was re-established with C (baseline, 0.1 mg/kg/inj) and doses of C (0.001-0.4 mg/kg/inj) or heroin (H, 0.001-0.1 mg/kg/inj) were available for the same number of sessions required for responding to decline to S levels and was stable. C and H were available in an alternating sequence separated by C baseline sessions to prevent development of H-induced physical dependence. Next, C (0.003-0.0125 mg/kg/inj, 3 doses) combined with H (0.001 or 0.006 mg/kg/inj) was made available. In all monkeys, inj/session for C increased as a function of dose. In three monkeys, the H dose-response was an inverted U-shaped function. One monkey did not take H above S levels. In two monkeys tested, C and H doses not self-administered above S levels when tested alone were self-administered above S levels when combined. These data suggest that combination of C and H resulted in enhanced reinforcing effects relative to either drug alone, which may be a mechanism of action for combined C and H (*i.e.,* "speedball") abuse in humans.

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EFFECTS OF HEROIN IN MONKEYS TRAINED TO DISCRIMINATE SALINE FROM COCAINE

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Interactions between the discriminative stimulus effects of heroin and cocaine were examined in rhesus monkeys. Five monkeys were trained to discriminate cocaine (0.4 mg/kg, i.m.) from saline in a two-lever, food-reinforced, drug discrimination procedure. Cocaine (0.013-1.3 mg/kg) produced a dose dependent generalization to the training dose of cocaine in all five monkeys, whereas heroin (0.032-1.0 mg/kg) produced a dose-dependent and complete generalization to cocaine in three of the five monkeys. The discriminative stimulus effects of cocaine were antagonized by the dopamine antagonist flupenthixol (0.018 mg/kg) but not by the opiate antagonist quadazocine (0.1 mg/kg). In contrast, the cocaine-like discriminative stimulus effects and rate decreasing effects of heroin were antagonized by quadazocine but not by flupenthixol. Pretreatment with heroin at doses that did not generalize to cocaine did not produce a consistent change in the cocaine dose-effect curve. Unlike heroin, the mu opiate agonists morphine (0.32-18.0 mg/kg), fentanyl (0.0032-0.056 mg/kg), nalbuphine (0.32-3.2 mg/kg) or TAMO (0.32-1.8 mg/kg) did not generalize completely to cocaine in any of the monkeys, although partial generalization was occasionally observed. Buprenorphine (0.01-1.0 mg/kg) generalized completely to cocaine in only one monkey. These results indicate that heroin mimics the discriminative stimulus effects of cocaine in some monkeys by acting at opiate receptors. These cocaine-like effects of heroin do not appear to involve an indirect stimulation of endogenous dopaminergic systems. Furthermore, heroin appears to have a greater ability than other mu opiate agonists to produce cocaine-like discriminative stimulus effects.

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BEHAVIORAL AND NEUROCHEMICAL CHARACTERISTICS OF A PHENTERMINE AND FENFLURAMINE DRUG MIXTURE IN RATS

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Clinical case studies suggest that combined administration of phentermine (PHEN) and fenfluramine (FEN) may be useful in the treatment of alcohol and cocaine addictions (Hitzig, *Maryland* Med *J* **42,** 1993). The present experiment examined the nature of the interaction between the two aminergic agonists using the drug discrimination paradigm to examine the quality of the subjective effects produced by the mixture and its similarity to other drugs of abuse (*e.g.,* cocaine, amphetamine, alcohol, etc.). *In vivo* microdialysis served to examine the neurochemical profile of dopamine and serotonin release in the nucleus accumbens. In conscious rats, intraperitoneal injection of FEN (1 mg/kg) or PHEN (1 mg/kg) selectivity increased serotonin and dopamine respectively. The mixture (1:1 ratio) increased both amines to a similar degree. Three groups of Sprague-Dawley rats were trained to discriminate saline from (1) FEN (1.0 rng/kg i.p.), (2) PHEN (1.0 mg/kg i.p.) and the mixture (3) PHEN + FEN (1:1 ratio) under a fixed ratio (FR-10) schedule of food reinforcement. The majority of rats trained on the mixture acquired the discrimination after 32±4 sessions. In comparison, the majority of rats trained to discriminate the individual compounds failed to meet criteria in 40 sessions, and thus the training dose was increased to 2 mg/kg. The individual compounds (1 mg/kg i.p.) generalized partially to the mixture, and complete generalization was observed following 3.0 mg/kg of FEN or PHEN. Rats trained to discriminate the individual components showed selective cross-generalization profiles. Cocaine (0.3-10.0 mg/kg i.p.), amphetamine (0.1-3.0 mg/kg i.p.) and nicotine (0.1-0.8 mg/kg s.c.) generalized to the mixture, but this was partial with no differences between FEN, PHEN, and MIX trained rats. No generalization was observed with alcohol and morphine. From the present results, it may be concluded that the two drugs given as a mixture do not produce a novel cue. Rather, these aminergics appear to interact additively. Furthermore, the dual stimulation of the amines by the mixture may be the basis for the cueing effects of the FEN + PHEN drug mixture.

SEQUENTIAL TRAINING OF DRUG DISCRIMINATION WITH DIFFERENT DRUGS: EFFECTS OF TRAINING HISTORY

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Pigeons were trained to discriminate pentobarbital from saline using a two-key procedure. After discrimination was established, the pentobarbital stimulus generalized completely to amobarbital and diazepam, partially to phencyclidine (PCP), but not to d-amphetamine or morphine. Subsequently, morphine discrimination training replaced pentobarbital training. After retraining to discriminate morphine from saline, the morphine stimulus generalized not only to other doses of morphine, but also to pentobarbital, diazepam and partially to PCP, but not to d-amphetamine or haloperidol. Subsequently d-amphetamine discrimination training replaced morphine training. After retraining to discriminate d-amphetamine from saline, the d-amphetamine stimulus generalized to other doses of d-amphetamine, morphine, pentobarbital, diazepam, and partially to PCP, but not to haloperidol. It appears that pigeons can remember previous discrimination training even when training with other drugs and a considerable period of time are interspersed between training and discrimination recall. It seems likely that drug addicts can also recall subjective drug effects for considerable time periods, even when other drug experiences are interspersed between exposures.

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PRE-EXPOSURE TO COCAETHYLENE CAN PRODUCE SENSITIZATION TO THE LOCOMOTOR ACTIVATING EFFECTS OF COCAINE

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According to the NIDA Household Survey, a majority of cocaine users are reported to use ethanol and cocaine simultaneously. The ethyl ester of benzoylecgonine, cocaethylene (CE), is a metabolite of cocaine formed in the presence of ethanol. CE is as potent as cocaine in inhibiting DA uptake, but less potent than cocaine as an inhibitor of serotonin uptake. CE has been shown to possess psychostimulant effects of its own. Most notably, CE serves as a potent reinforcer in laboratory animals. However, it was unclear as to whether sensitization develops following repeated intermittent exposures to CE. The present study investigated the ability of CE to produce cross-sensitization to cocaine. Male Sprague-Dawley rats were given five daily injections of CE or cocaine (15 mg/kg, base weight, i.p.). Following a seven day drug free interval, subjects were challenged with cocaine and assessed for locomotor activity using automated photocell arenas. In addition, blood plasma and brain tissue levels of each drug were determined following cocaine or CE administration using HPLC. Preexposure to either cocaine or CE produced cross-sensitization to the locomotor activating effects of a 15 mg/kg challenge injection of cocaine relative to saline-preexposed controls. Striatal drug levels were not significantly different following cocaine or CE (15 mg/kg, base weight, i.p.) administration. However, significantly higher plasma levels of cocaine relative to CE were observed. These data suggest that CE can produce sensitization to the locomotor activating effects of cocaine and that differences in the bioavailability of the drugs may at least in part account for subtle differences in the ability of CE to produce sensitization relative to cocaine as reported in our previous studies.

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THE EFFECTS OF ALCOHOL ON THE DISCRIMINATIVE PROPERTIES OF COCAINE

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Alcohol has recently been reported to potentiate the effects of cocaine within a number of behavioral and physiological preparations. The present experiment examined this interaction within a drug discrimination procedure in which dry tube licking was differentially reinforced following the administration of cocaine or its vehicle. Specifically, six Long-Evans female rats were trained to discriminate cocaine (10 mg/kg) from its vehicle under a FR20 schedule of water reinforcement. Following acquisition of the discrimination generalization tests were performed to assess the level of drug-appropriate responding to various doses of cocaine. The effects of alcohol on cocaine-appropriate responding were dose dependent. Group data illustrate that when cocaine was combined with 0.56 g/kg alcohol, cocaine-appropriate responding decreased; when combined with 0.75 g/kg alcohol, cocaine-appropriate responding increased. Data from individual subjects, however, did not consistently support these group trends. Although the combination of cocaine and 0.56 g/kg alcohol suppressed cocaine-appropriate responding, only in three of eight cases did the combination of cocaine and 0.75 g/kg alcohol increase it. For both doses of alcohol in combination with cocaine, responding, in a majority of the other cases, was either suppressed or unaffected. Although the present data appear not to support the position that alcohol potentiates the stimulus properties of cocaine, the combination of alcohol with doses of cocaine may produce a stimulus different from that of the training condition, thus resulting in greater vehicle-appropriate responding.

PHARMACOKINETICS OF COCAETHYLENE AND ITS METABOLITES IN PLASMA AFTER COCAINE AND ALCOHOL ADMINISTRATION

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The aim of this investigation was to study the metabolic profile of cocaethylene (CE) generated after the administration of cocaine (CO) and alcohol. It has been suggested that the increased hepatotoxicity observed in those consumers of CO and alcohol might be related to a higher rate of oxidative metabolism of CO and CE when compared with the situation where cocaine is ingested atone.

Eight healthy recreational users of cocaine participated in a clinical trial designed to study cocaine and alcohol interactions. Subjects received randomly cocaine 100 mg (snorted), ethanol 0.8 g/kg (as a beverage), both substances and placebo. Blood samples at different times were collected until 24 h to determine: CO, benzoylecgonine, ecgonine methyl ester, CE, norcocaine (NC) and norcocaethylene (NCE). Analysis were performed by GC/MS using deuterated analog standards. CO and NC concentrations were higher in the combination group. CE and its metabolite (NCE) only appeared in the combination group. The rate of metabolic transformation by oxidative N-demethyladon of CE (NCE) was higher in comparison to the transformation of CO (NC).

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COCAINE, ALCOHOL, AND COCAETHYLENE EFFECTS IN HUMANS: FINDINGS FROM A REPEATED DOSE STUDY

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Binge use is a common practice of cocaine abusers and comorbid alcoholism is common. This study attempts to more closely approximate street use of these substances to examine behavioral and physiological effects of combined cocaine and alcohol use and the role of the active metabolite, cocaethylene. Six subjects (two females) meeting DSM-III-R criteria for cocaine dependence and alcohol abuse participated in this randomized, double-blind, placebo-controlled, within-subjects study with three sessions (each 480 min): four doses of intranasal (i.n.) cocaine (C) (1 mg/kg) every 30 minutes with oral ethanol (E) (1 g/kg) administered following the initial C dose and a second E drink (120 mg/kg) at +60 minutes to maintain plasma E concentration during C administration, C doses with placebo E, and C placebo with E. Area under the curve (AUC) values representing responses to successive doses of C and residual effects were analyzed using a two-factor repeated measures ANOVA. $p<.10$ (one-tailed) was considered significant. Plasma C concentration during cocaine/ethanol (CE) administration significantly exceeded that for C administration. Cocaethylene concentrations ranged from 22-40% that of C. Heart rate was significantly increased following each dose of study drug for CE administration relative to C or E alone ($p<.05$). "Any High" was significantly greater for CE administration relative to C for each dose ($p<.10$), and E following dose three. Means for "Cocaine High" were greater during CE. Ratings for "Feel Good" were significantly greater for the CE condition relative to C or E for all doses ($p<.05$). Repeated doses of cocaine with alcohol produce higher cocaine concentrations, substantial cocaethylene concentrations relative to cocaine, enhanced "high", and increased heart rate relative to cocaine or alcohol alone. Cocaethylene, with its greater concentration at later times, may play a role in potentiation of effects. Cocaine/ethanol enhances the perception of "feeling good", particularly at later time points which might perpetuate binge use contributing to morbidity and mortality.

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NEUROPSYCHOLOGICAL FUNCTIONING IN CHRONIC COCAINE AND ALCOHOL ABUSERS

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Thirty chronic cocaine and alcohol abusers were compared with age, education, race and sex matched chronic cocaine abusers (n=30) and normals (n=30) using the extended Halstead-Reitan Neuropsychological Test Battery to determine whether abusers of cocaine and alcohol in combination were more impaired than abusers of cocaine alone. The data were analyzed with MANOVA and ANOVA, and with nonparametric analyses when achievement of normality was not possible. Cocaine and alcohol abusers did not differ from normals on the majority of test measures. An unexpected but consistent finding was the poorer performance of the cocaine sample relative to cocaine and alcohol abusers on measures of complex psychomotor and simple motor functioning [$F(2,87)=3.15$, $p<0.0005$; $F(2,87)=3.48$, $p<0.0001$]. Pure cocaine abusers also performed more poorly than normals on a measure of global neuropsychological functioning [$X^2=8.91$, $p<0.01$]. A second unexpected finding was the superior performance of the cocaine sample on a test of attention [$F(2.87)=18.22$, $p<0.0001$]. Results were consistent with previous reports of generally mild cognitive dysfunction in cocaine abusers, who also demonstrate supranormal skill on certain tests of vigilance. Results also suggested that cocaine and alcohol abusers of relatively young ages may be less cognitively impaired than matched cocaine abusers. Evidence from studies of vascular functioning in abusers of cocaine and alcohol alone and in combination is discussed as possible explanation for these findings.

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IMPAIRMENT OF REFLECTIVE PROCESSING AFTER ACUTE ALPRAZOLAM AND AMPHETAMINE ADMINISTRATION

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In a previous study, we compared drug abusers, not under the influence of any drug, with normal controls on a series of tests assessing cognitive functioning. On most tests, there were no differences between the two groups; however, drug abusers demonstrated a selective failure in reflective processes by making a greater number of intrusion errors on a test of delayed free recall of a list of categorically-related words. We hypothesized that this inability to inhibit inappropriate responses would be exacerbated by an acute drug challenge. To test this hypothesis, we administered d-amphetamine (0, 12.5, and 25 mg) to current stimulant users (n=8) and alprazolam (0, 1, and 2 mg) to current sedative users (n=7). Subjects received each drug dose twice in random order, and test sessions were conducted at least 72 hours apart. At predrug baseline and two postdrug times (two and four hours for d-amphetamine; one and three hours for alprazolam), subjects were read a list of 12 categorically-related words, six of which were repeated twice. After 15 minutes of intervening tests that prevented rehearsal, subjects were asked to recall the words in any order. Different word lists were used at each time and dose. Working memory was assessed by identification of repeated words as they were read. Explicit memory was measured by the number of correctly recalled words during free recall, and inhibitory functioning was assessed by the number of intrusion errors during free recall. Alprazolam impaired working memory, explicit memory, and inhibitory functioning by increasing the number of intrusion errors. *d*-Amphetamiue also increased intrusion errors, but had no effect on working memory and explicit memory. This selective effect of *d*-amphetamine on reflective processing suggests that the inability to inhibit inappropriate responses (*i.e.,* reflective processing) is not simply due to drug-induced sedation, but may reflect a general adverse consequence of drugs of abuse.

SEDATIVE USE IN OPIATE DEPENDENT PATIENTS: ASSOCIATION WITH PSYCHIATRIC AND OTHER SUBSTANCE USE DISORDERS

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This study characterized substance use patterns and psychiatric profiles of opiate dependent patients in relation to their status on sedative use disorder diagnosis. Patients were 231 consecutive admissions to opiate substitution treatment (*i.e.,* methadone, LAAM, or buprenorphine). Lifetime psychiatric and substance use disorders were determined using the Structured Clinical Interview for the DSM-IIIR (SCID). Forty percent (94/231) of the patients were negative for a lifetime sedative use disorder (HX-), 39% (89/231) had a past disorder (HX+), and 21% (48/23 1) had a current (CUR+) disorder. Several group differences were found. Both the HX+ and CUR+ groups were more likely to be white than black (61% and 67% white versus 21% white in HX- group). The HX+ and CUR+ groups also had a greater number of lifetime drug use diagnoses (means= 4.5 and 4.3, respectively) than the HX- group (3.2) including higher rates of alcohol, cannabis, stimulant, cocaine and hallucinogen use disorder. In contrast, prevalence of other psychiatric disorders (including anxiety and depression) was low and did not differ across groups, with the exception of higher rates of Antisocial Personality Disorder in both the HX+ (41.6%) and CUR+ (35.4%) than in HX- (22.3%) groups. These results suggest that sedative use disorder in opioid abusers is related more to a severe spectrum of drug dependence and multiple drug abuse than it is to the self-medication of an underlying mood or anxiety disorder.

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RELATIONSHIP OF TOBACCO AND MARIJUANA SMOKING CHARACTERISTICS TO INITIATON OF REGULAR COCAINE SMOKING

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To determine the relationship between the increasingly prevalent smoking of crack cocaine (C) and the well-established habits of tobacco (T) and marijuana (M) smoking, we examined the responses of 228 regular smokers of C (age 42 ± 8 years) (cases) to a detailed drug use questionnaire as part of an ongoing study of the pulmonary effects of habitual C smoking. Cases smoked 7.0 ± 12.7 [SD] g/week of C for 52 ± 40.2 months 9 cases had never smoked T or M, 39 had smoked T hut not M, 40 had smoked M but not T, and 140 regularly smoked both T and M. Cases were compared with 64 non-C smoking controls matched for gender, age and race with respect to T and M smoking behavior. Results: T, but not M, smoking histories were similar for cases and controls. While C smokers had a mean lifetime amount of M smoking (joint-years) 3X that of non-C smokers ($p<.0001$, t-test), C smokers who still smoked M at the time of the interview were smoking on the average 1/2 the amount of M of the non-C smokers. Among C smokers one year after compared with one year before initiation of habitual C smoking, T smoking did not change in 85%, but M smoking declined in 41% (by 3.7 ± 5.8 joints/week). Of those who smoked T and/or M, 97% did so before their first experience smoking C. Only 10% of C smokers who quit T smoking, in contrast to 40% of C smokers who quit M smoking, did so at or after initiation of regular C smoking. Conclusion: After initiation of regular C smoking, pre-existing M use generally declined while T use remained unchanged. It is not clear from these data whether the decline in M use was caused by initiation of regular C smoking or whether C smoking was begun as a replacement for an independently declining M habit, but the relationship between M and C smoking does not appear to carry over to T smoking.

CIGARETTE SMOKING AND OPIATE USE COVARY: AUTOCORRELATIONS IN OPIOID-MAINTAINED PATIENTS

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The primary hypothesis in this preliminary study proposed that opioid and nicotine use by opioid-dependent patients (DSM-III-R) is interdependent. The interdependence of the opioid and nicotine urine analyses was evaluated using the moving average model of Box-Jenkins time series analysis (Box and Jenkins 1976). Autocorrelations were derived through the accumulation of weighted averages of sequential sets of paired semiquantitative urine levels of morphine and cotinine, and methadone and cotinine. In a study done at the L.A. Treatment Research Unit, the first 1,000 urines, collected over six months, from 41 subjects enrolled in a random-assignment, double-blind, outpatient comparative trial of 30 mg methadone (N=15), 80 mg methadone (N=13) and 8 mg buprenorphine (N= 13) were assessed for urine analytes of heroin and other opiates, methadone, and nicotine (cotinine). Comparisons utilizing t-tests or chi-square analysis showed no significant demographic differences between the different groups. Eighteen subjects, each of whom had 14 or more clinic visits and were positive for morphine and/or methadone, accounted for the majority (671) of the 1,000 urines. Since buprenorphine analysis was not performed, only those patients receiving buprenorphine with urines positive for morphine were subjected to statistical analysis. Results from the 671 urines were subjected to Box-Jenkins time series analysis to determine each subject's same day (zero lag) autocorrelation value of morphine and cotinine and/or methadone and cotinine. Each of the 18 subjects demonstrated positive autocorrelations between morphine and cotinine levels (N=7; range: 0.30 to 0.56; median=0.40) and/or between methadone and cotinine levels (N=15; range: 0.19 to 0.74: median=0.34). Both sets of results were significant at $p<0.01$ by sign test. These findings suggest a coordination of opioid use and cigarette smoking, and that analysis of semiquantitative urine levels by Box-Jenkins time series analysis may accurately monitor the complex interactions of polysubstance abuse. We suggest that systematic pharmacological stabilization of nicotine in the presence of maintenance opioid administration (*e.g.,* nicotine patch and methadone) may together yield better results in diminishing use of illicit opioids such as heroin when compared to opioid maintenance alone.

ATTRIBUTIONS FOR USING COCAINE, OPIATES, ALCOHOL, AND NICOTINE

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Thirty-eight crack-cocaine users, 22 methadone-maintained opiate users, 16 alcoholics, and 45 cigarette smokers were asked to estimate the percentage of time they used their preferred substance (a) "to get rid of bad feelings or moods", (b) "to get rid of withdrawal", (c) "to boost the pleasure from other activities", and (d) "to get special good feelings such as a high". These categories were queried with regard to three time intervals: initiation of regular use, current use, and relapse after a month of abstinence. INITIATION: All users attributed their initial use to desiring the high and to boosting pleasure from other activities. CURRENT USE: Current users added reduction of negative moods to their reasons for use, and opiate users and smokers also cited withdrawal as a reason for use. RELAPSE: Contrary to popular conceptions that pharmacological withdrawal may drive users back to the drug after a period of abstinence, users did not cite withdrawal as important. Instead, all users attributed relapse to a positive motivation: cocaine, opiate users, and alcoholics attributed relapse to desiring the drug high, smokers attributed relapse to boosting pleasure. These findings have implications for the development of medications for the treatment of substance abuse: those which block pharmacological withdrawal may help break a current cycle of use, but may not be important in preventing relapse. Relapse prevention treatments should include interventions which help patients develop alternative sources of pleasure and which address problematic negative mood states.

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BUPRENORPHINE FOR TREATMENT OF DUALLY-DEPENDENT (OPIATE AND COCAINE) INDIVIDUALS

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This study evaluated the safety and efficacy of four different dose schedules of sublingual buprenorphine for treatment of outpatients who met DSM-IIIR criteria for both opiate and cocaine dependence. Two-hundred dually dependent outpatients (mean age 34.0 ± 6.4 years, 76% African-Americans, and 66% males) received weekly individual drug abuse counseling plus buprenorphine at doses of 2, 8, or 16 mg/day, or 16 mg every-other-day for ten weeks, using a double-blind, placebo-controlled, random assignment design, and stratifying by gender and age (21-35 and 36-50). The medication was well tolerated by patients, and no serious side-effects were observed. Comparisons among groups showed no differences in retention in treatment and self-reported weekly use of cocaine or heroin, with all groups showing reductions. However, after five weeks of treatment, the group that received 16 mg of buprenorphine every day showed a greater reduction of urines positive for cocaine than the other three groups. These results show that buprenorphine: 1) is safe at the doses provided here, 2) in combination with counseling is effective for treatment of dual dependence (heroin and cocaine), even at the lowest dose (2 mg qd), and 3) at the highest dose (16 mg qd) may be more effective for treatment of cocaine dependence.

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LONGITUDINAL DOSE COMPARISON OF BUPRENORPHINE FOR COMBINED OPIATE AND COCAINE DEPENDENCE

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Buprenorphine's efficacy for treatment of combined intravenous heroin and cocaine dependence was studied over twelve months in a multiple dose, placebo controlled design. Method: Subjects were men with DSM-IIIR concurrent intravenous opiate and cocaine dependence. After admission to an inpatient treatment research unit and randomization to daily doses of sublingual buprenorphine 4 mg or 8 mg in single blind fashion, or 12 mg or placebo in double blind fashion, completers were offered outpatient maintenance for up to 52 weeks. Numbers of clean urines over time were analyzed with the Generalized Estimating Equations model, conservatively inputing noncompliance and dropout as "dirty". Results: Forty-four patients completed an average of 29 weeks of outpatient buprenorphine maintenance. Mean duration of drug use was 12.2 years for opiates and 11.2 years for cocaine and the four treatment groups revealed no significant differences on most demographic and baseline variables. Significant findings were that buprenorphine treatment was superior to placebo for both heroin and cocaine dependence, 4 and 8 mg were superior to 12 mg, all groups experienced decrements in the numbers of clean urines over time, and this change was greatest for placebo and buprenorphine 12 mg. Conclusions: Buprenorphine efficacy and tolerance may follow a U-shaped dose response curve.

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DESIPRAMINE AUGMENTATION OF BUPRENORPHINE FOR COCAINE ABUSE

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Recent studies have suggested that desipramine (DMI) and buprenorphine (BUP) may reduce cocaine abuse. In a 26 week double blind, placebo controlled, randomized clinical trial of 141 opioid and cocaine dependent subjects we compared methadone (MTH) (65 mg) to BUP (12 mg sl) combined with DMI (150 mg) vs placebo (P) in a three month cross-over. The four groups (MTH/DMI vs MTI-VP vs BUP/DMI vs BUP/P) were demographically comparable and had similar treatment retention (18 weeks). Endpoint analyses adjusting for baseline cocaine use found a significantly greater improvement in cocaine free urines for BUP/DMI versus all other treatments ($F=4.4$; $df=1,136$; $P<0.05$ for DMI and $F=3.5$; P,0.05 for BUP by DMI interaction). At endpoint the least squares adjusted rates of cocaine free urines were: BUP/DMI 53%, BUP/P 31%, MTH/DMI 38%, MTH/P 38%. The BUP/DMI subjects (GPI) during the first 13 weeks went from 20% to 60% cocaine free urines, while the BUP/P (GP2) went from 28% to 32%. The subjects then crossed-over to P or DMI respectively, and GPI maintained their 60% "clean" urines and GM improved from 25% to 45% cocaine free urines. DMI blood levels averaged 136 (sd=105) ng/ml with levels above 350 ng/ml associated with poor outcomes. Thus, DMI augmentation of BUP appears to improve cocaine abuse significantly.

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OUTCOME OF COCAINE INPATIENT DETOXIFICATION

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Although methadone maintenance treatment is effective in eliminating or reducing opiate use, significant proportions of opiate addicts entering methadone programs are also addicted to cocaine and continue to use cocaine during treatment. Cocaine use among methadone patients has been associated with greater HIV risk, criminal activity, and poor treatment outcomes. One standard response to cocaine use has been inpatient detoxification. However, there is very little evidence on the efficacy of this intervention. This study examined the effectiveness of inpatient cocaine detoxification by comparing pre- and post-treatment urine toxicologies for methadone patients who had been hospitalized for cocaine withdrawal. In this study the unit of analysis is the hospital admission episode (N = 77). During the twelve weeks prior to detoxification, all admissions had at least one cocaine-positive urine. At post- detoxification *admissions* with at least one cocaine positive urine were 82% at one to four weeks and 91% at 1 to 12 weeks. The proportion of *tests* positive for cocaine in the 12 weeks before detoxification was .82, while at post-detoxification the proportion of tests positive was .57 at one to four weeks, and .60 at 1 to 12 weeks (both $p < .001$). These results show a negligible effect on abstinence and a statistically significant, although modest, reduction in the frequency of cocaine use (a 25% decline in positive urines during post-treatment weeks 1 through 12). Cocaine use after detoxification resumes rapidly and at almost the same level as before detoxification. These findings raise serious doubts about the cost-effectiveness of inpatient cocaine detoxification. The very limited change in these patients points to a need to consider alternative treatments that may be more cost-effective.

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ELAPSED TIME SINCE LAST USE: VARIABLE CHARACTERISTICS AND ANALYTICAL RESULTS

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The analysis addresses properties and characteristics of self-reported elapsed time in hours from last cocaine use to assessment point as an outcome measure. Minimizing demands on subjects memory and relatively unambiguous, it was hypothesized that its distribution would serve as a useful descriptor of study subjects and correlate with other measures of cocaine use. Data for this analysis comes from 13 weekly assessments of 44 subjects who participated in a previously described trial of fluoxetine in the treatment of cocaine addiction in methadone-maintained subjects. Mean elapsed time ranging from 30.8 to 134.6 hours and median times of 17.75 to 39.5 hours. Correlations with both plasma and urine levels of cocaine and benzoylecognine were negative in sign and most were statistically significant. Degree of correlation among assessments varied. Improved characteristics were obtained using a base-10 logarithm transformation. Treatment group differences, similar to previous overall study outcome, were also found. Issues of imputing missing data are discussed.

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FUNCTIONAL ROLE AND SEQUENCE ANALYSIS OF A LYMPHOCYTE ORPHAN OPIOID RECEPTOR

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Biochemical and pharmacologic evidence indicates that lymphocytes express opioid receptors. By DNA sequencing of reverse transcription-polymerase chain reaction products, we have found that mouse splenic lymphocytes express mRNA encoding an orphan opioid receptor. These mRNA transcripts were detected in $CD4^+$, $CD8^+$, and $CD4^-$ $CD8^-$ lymphocyte subpopulations. Northern blot analyses confirmed that splenic lymphocytes Y^{71} -R^{75} in the intracellular loop are alternatively spliced, suggesting that orphan opioid receptor mRNA encodes two receptor subtypes. In preliminary experiments, full length orphan opioid receptor-transfected COS cells exhibited norbinaltorphimine-displacable ethylketocyclazocine binding while truncated orphan opioid receptor-transfected COS cells and non-transfected COS cells showed no specific binding. Treatment of lipopolysaccharide-stimulated splenic lymphocytes with orphan opioid receptor antisense oligonucleotides suppressed polyclonal IgM evidence that lymphocytes express an opioid-like receptor gene, and suggest that this receptor plays a functional role in immunocompetence.

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MORPHINE SENSITIZES TO INFECTION WITH *LISTERIA MONOCYTOGENES*

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Implantation of a 75 mg morphine (M) pellet sc suppressed the capacity of spleen cells of C57BL/6J mice to make an *in vitro* plaque-formingcell response to sheep red blood cells. Naltrexone blocked the immunosuppression. Previous studies in C3HeB/FeJ mice showed that macrophages of M-pelleted mice had defective function, as did macrophages that were treated with M *in vitro.* The present experiments were designed to assess of drug administration on resistance to infection in C57BL/6J mice with an intracellular pathogen that parasitizes macrophages, *Listeria monocytgenes.* Mice that were given M pellets and infected ip 48 hours post-implantation were markedly sensitized to Listeria infection (6% survival versus 95% survival in placebo-pelleted mice). Simultaneous implantation of a naltrexone pellet protected animals against the effect of M (85% survival). To verify that mortality induced by M was due to enhanced *in vivo* growth of Listeria, groups of mice implanted with M pellets, placebo pellets, naltrexone pellets or M + naltrexone pellets were infected with Listeria. At various times post-infection, groups of animals in each treatment regimen were sacrificed, and their livers were homogenized and plated on bacteriologic medium to determine the number of organisms present. It was found that M-pelleted mice had over 200-fold greater numbers of Listeria at 42 hours post-infection than M + naltrexone treated animals or other types of controls. These results show that M sensitizes to infection with *Listeria monocytogenes.* The mechanism of sensitization involves opioid receptors, as naltrexone blocks the effect.

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INHIBITION OF MACROPHAGE CYTOKINE PRODUCTION FOLLOWING TREATMENT WITH A KAPPA OPIOID AGONIST

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Previous work in our laboratory showed that μ-opioid agonist such as DAMGE and Morphine, and the κ-selective agonists U50,488H and U69,593 are all able to inhibit antibody production *in vitro*. Our present interest is to further determine which immune cell populations are being affected by opioid treatment and to determine specifically which opioid receptor type is expressed on these cells. In this study, non-elicited peritoneal macrophages from Balb/c mice were treated simultaneously with the κ--agonist U50,488H and LPS, and the levels of the cytokines IL-1, IL-6 and TNF-α were measured to determine whether the monocyte/macrophage population is a target of opioid modulation. The results showed that U50,488H had a suppressive effect on the production of TNF-α and IL-1 at concentrations as low as 10^{-9}M, while IL-6 was suppressed with concentrations as low as 10^{-8}M. Additional experiments utilizing the opiate antagonist naloxone and the κ--selective antagonist nor-binaltorphimine (nor-BNI) were performed in order to further characterize the opioid receptor involved in the cytokine suppression by treatment with U50,488H. Results showed that naloxone was able to partially block US0,488H suppression while nor-BNI was able to completely reverse the suppression of IL-6 production. These results suggest that macrophage/monocyte function is significantly modulated following interaction with the κ-opioid compounds.

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EFFECTS OF SELECTIVE μ-, κ- AND δ-OPIOID ANTAGONISTS ON INTER- LEUKIN-10 (IL-1ß)-INDUCED HYPERTHERMIA

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IL-10 is a cytokine present within the brain that produces marked hyperthermia and alters activities of thermosensitive neurons when it is administered into the preoptic anterior hypothalamus (POAH), a primary central control site for body temperature (Tb) regulation. We have reported that μ opioid receptor agonists given into the POAH elicited hyperthermia. In the present study, using intraPOAH microinjection of selective opioid receptor antagonists, we investigated whether endogenous opioids and involved in the intraPOAH-IL-1ß-induced hyperthermia and which type of opioid receptors might mediate this effect. Male S-D rats were implanted with a 23-gauge guide cannula unilaterally into the POAH under anesthesia. The selective μ opioid receptor antagonist CTAP, κ opioid receptor antagonist nor-BNI, δ opioid receptor antagonist naltrindole (NTI) or the general opioid receptor antagonist naloxone (Nal), all of which lack significant effects on Tb by themselves when given into the POAH, were microinjected into the POAH 30 min before IL-10 microinjection into the same region. IL-1ß (5-1000 U) alone caused a dose-dependent hyperthermia (ΔTb: 0.9-2.2 °C) lasting about five hours with a peak Tb response at 120 minutes. Hyperthermia caused by IL-1ß (5 U) was completely blocked by the intraPOAH pretreatment with CTAP (2.5 μg) or Nal (10 μg). Hyperthermia caused by IL-1ß can also be reduced by pretreatment with Nal (10 mg /kg) injected s. c. and completely blocked by three consecutive s. c. injections of Nal (10 mg / kg / h) at one hour intervals. Pretreatment with NTI (0.25-0.5 μg) attenuated only the later phase of IL-1ß-induced hyperthermia. Nor-BNI did not affect the Tb response caused by IL-1ß These data suggest that endogenous opioids arc involved in the hyperthermic effect of intraPOAH IL-1ß and the IL-1ß induced hyperthermia appears to he mediated primarily through μ opioid receptors within the POAH.

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REGULATION OF POMC GENE EXPRESSION IN RAT PITUITARY, HYPOTHALAMUS AND AMYGDALA BY CHRONIC ADMINISTRATION OF CRH, DEX AND METHADONE

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Based on clinical research on methadone maintenance in the treatment of heroin addiction, we hypothesized that there is a normalization, rather than disruption, of the neuroendocrine system during steady state administration of the exogenous opioid methadone, which is long-acting in humans, but short-acting in rat. We measured the levels of pro-opiomelanocortin (POMC) mRNA in the hypothalamic-pituitary axis of the rat using a modified solution hybridization protection assay, comparing the known effects of corticotropin-releasing hormone (CRH) and dexamethasone (DEX) on pituitary POMC mRNA with the effects of steady state methadone, and also the effects of all three on POMC mRNA in the hypothalamus (Hyp) and amygdala (Amy). Repeated twice daily i.p. injections of human CRH (100 ug/kg/d) for five days resulted in a 85% increase in POMC mRNA levels in the anterior lobe (AL) ($p<0.001$), but had no effect on POMC mRNA in the neurointermediate lobe/posterior lobe (NIL/PL), Hyp or Amy. The synthetic glucocorticoid DEX (400 ug/rat/d, i.p.) caused a 40% decrease in POMC mRNA levels in the AL ($p<0.005$) and a 37% decrease in the NIL/PL ($p<0.05$), but had no effect on POMC mRNA levels in the Hpy and Amy. A steady state administration of methadone by mini-osmotic pump for seven days (10 mg/kg/d) had no effect on POMC mRNA levels in the AL and NIL/PL of the pituitary or in Hyp or Amy. These observations demonstrate that: (1) chronic CRH administration up-regulated POMC gene expression selectively in the AL: (2) chronic DEX administration down-regulated POMC gene expression only in the AL and the NIL/PL: and (3) chronic treatment with methadone did not alter POMC gene expression in the pituitary or in the brain regions studied.

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THE EFFECTS OF MORPHINE IN A TRANSGENIC MOUSE MODEL OF IMPAIRED CORTICOSTEROID RECEPTOR FUNCTION

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It is suggested that the hypothalamic-pituitary-adrenocortical (HPA) axis is, at least partly, the biological substrate of the individual differences in the sensitivity towards abused drugs. Thus, we studied a transgenic mice model with impaired corticosteroid receptor function resulting in a dysfunctional glucocorticoid feedback. Since morphine-induced locomotor stimulation is positively correlated with the rewarding effects of morphine, morphine-induced locomotor activity of transgenic mice and control non-transgenic mice (B6C6F1) was examined. Morphine-induced locomotor activity depends on an intact mesolimbic system, therefore, dopamine (DA) release and metabolism was also measued within the mesolimbic system. Results indicate that basal activity and also activity following vehicle injection do not differ between these two mouse lines. Morphine (7.5-15 mg/kg; i.p.) dose-dependently increased motor activity for three hours in control and transgenic mice as compared to vehicle injections, however, morphine-induced locomotion was significantly more pronounced in transgenic mice. Further rnorphine-induced mesolimhic DAergic activity was enhanced in transgenic animals as compared to controls. These results parallel endocrine data showing that the corticosterone and ACTH plasma levels of transgenic mice reach higher values to those observed in control mice following morphine injections. In conclusion, this transgenic mouse line shows an enhanced psychomotor-stimulant effect to morphine, a response which is mirrored by an enhanced DAergic activity within the mesolimbic system. In summary the described dysregulation of the HPA axis in the transgenic mice might contribute to an enhanced vulnerability to a drug-seeking behavior.

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EFFECTS OF ACUTE AND REPEATED INTRANASAL COCAINE ON PLASMA PROLACTIN LEVELS IN HUMAN DRUG USERS

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It is well established that prolactin (PRL) secretion is tonically inhibited by dopamine (DA) released from nerve terminals in the mediobasaJ hypothalamus. Interestingly, some investigators have noted hyperprolactinemia in abstinent cocaine addicts, and this phenomenon is suggestive of cocaine-induced impairment in central DA function. Since cocaine is known to inhibit DA reuptake, we hypothesized that acute cocaine treatment would decrease circulating PRL. in human subjects. In the present study, the effect of cocaine administration on plasma PRL was examined in male polydrug abusers (N = 18) who met DSM-IV criterion for cocaine dependence. Subjects resided on the ARC research ward and participated in two test sessions per day (AM and PM) for five consecutive days. Subjects "snorted" both placebo (4 mg cocaine/96 mg lactose) and cocaine (96 mg cocaine/4 mg lactose) each day, with cocaine being presented in a randomized, double-blind fashion at one of the daily sessions. Repeated blood samples were withdrawn during sessions on days one and five. In addition, endocrine challenge tests were performed using the DA receptor agonist pergolide (0.1 mg, p.o.) five days before and three days after the repeated cocaine regimen. Intranasal cocaine had no significant effect on plasma PRL at any session. Basal PRL levels were within normal range at the beginning of the study and did not change with repeated cocaine dosing. Administration of pergolide caused a decrease in circulating PRL that was similar before and after the period of cocaine exposure. Thus, our results provide no evidence for alterations in DA neurotransmission following acute or repeated cocaine administration. The failure of cocaine to suppress PRL secretion in the present study raises questions concerning the role of DA in mediating the pharmacological effects of cocaine in human subjects.

THE EFFECTS OF ACUTE AND CHRONIC ANABOLIC ANDROGENIC STEROID (AAS) TREATMENT ON LOCOMOTOR STIMULANTS

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Potential pharmacological interactions may occur in individuals whose abuse steroids as well as other illicit drugs. The effects of testosterone propionate (TES) treatment on differing classes of stimulants and the effect of nandrolone propionate (NAN) on cocaine induced locomotion were evaluated. Male ICR mice were treated (i.p.) acutely or chronically (4 weeks) with testosterone propionate or sesame oil (veh). An hour after the acute or last chronic TES injection, mice were administered various stimulants and evaluated for locomotor stimulation. Dose response curves were generated for cocaine (COC), amphetamine (AMP), amfonelic acid (AFA) and caffeine (CAF) following acute AAS treatment and for COC following chronic AAS treatment. The E_{max} and ED_{50} were determined from the stimulatory portion of the dose response curves utilizing sigmoidal curve linear analysis. NAN was evaluated under acute conditions with the stimulant COC but a full dose response curve was not generated. Acute TES treatment significantly reduced the E_{max} (counts) of COC (7016 to 4492), AFA (8369 to 5825), and AMP (8235 to 4818) but not CAF (3501 to 3300). Chronic AAS treatment did not significantly reduced the E_{max} of COC (8342 to 7008). The ED_{50} values of treatment groups did not differ from controls. NAN attenuated the maximal locomotor effects of cocaine under the acute treatment condition. Acute TES decreases the maximum stimulatory effect of dopaminergic-stimulants. The stimulant caffeine was not altered suggesting the pharmacological activity of TES is specific for dopaminergic stimulants verses. NAN inhibited cocaine mediated increases in locomotor activity. This result suggest this phenomenon will be seen with all AAS drugs. Chronic treatment with TES produced a significant attenuation of the decrease in locomotor activity seen in the acute cocaine study suggesting a molecular mechanism behind the steroid influence on locomotion stimulants. The interaction that exist between stimulants and steroids in polydrug abusing humans is unknown and further studies (are necessary to elucidate a mechanism of action.

A PILOT EVALUATION OF ANABOLIC STEROID USERS ACROSS AND BETWEEN CYCLES OF USE

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Various side effects possibly related to anabolic steroid (AS) abuse have been reported; however, serious medical side effects seem to be rare. Psychological and psychiatric morbidity in AS users has also been reported, and may be more common than other side effects. Lacking in research results reported to date has been a prospective analysis of the behavioral effects of high-dosages of ASs when these drugs are self-administered in a manner typically seen in weightlifters, bodybuilders, and others seeking gains in muscular strength and personal appearance. Such an examination was addressed in the present, ongoing study conducted at the University of Pennsylvania Treatment Research Center. Subjects are six male, paid volunteers who reported administering numerous ASs both orally and parenterally. Subjects returned to the research facility at approximately two week intervals to complete various behavioral and drug use questionnaires, provide blood and urine samples for clinical and toxicological analyses, and undergo medical and psychiatric/psychological evaluations. Subjects' reports regarding four effects (changes in aggression, libido, frequency of sexual activity, and mood swings) indicated that increases in these effects were reported two to ten times more often than decreases when subjects were on a cycle of AS use compared to when they were not. In addition, data from the Beck Depression Inventory, Profile of Mood States questionnaire, and the Buss-Durkee Hostility Scale indicated changes in these scale scores across time. However, these changes were not always clearly related to periods of reported AS use, and life events (*e.g.,* relationship problems, gambling losses) also appeared to impact on scale scores. Further, additional factors *(e.g.,* subjects' other drug use, the use of long-acting AS preparations) may have inlluenced the observed results. Urine assays generally supported subjects' reported AS use. Following completion of the study, analyses will focus on assessing intra- and inter-individual differences in an effort to elucidate those factors which influence the continued use of ASs and to identify specific AS-related effects.

EFFECTS OF SUPRAPHYSIOLOGIC DOSES OF TESTOSTERONE ON HUMAN AGGRESSIVE AND NON-AGGRESSIVE RESPONDING

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The present study was conducted to assess the effects of supraphysiologic doses of testosterone on human aggressive responding in a controlled laboratory setting. Male subjects between the ages of 23-38 received gradually increasing doses of testosterone cypionate (150 mg/week for two weeks, 300 mg/week for two weeks, and 600 mg/week for two weeks) or placebo using a double-blind, randomized, cross-over design. Subjects were tested both before and after the series of i.m. injections. During each 20-minute experimental session (Point Subtraction Aggression Paradigm: Cherek *et. al.,* 1985) subjects could press a button to accumulate points exchangeable for money (non-aggressive response) or press another button to subtract points from a fictitious person (aggressive response). Aggressive responding was instigated by subtracting points from the subject which were attributed to a fictitious opponent. To maintain the illusion of a human opponent, periods free of point subtractions or provocations occurred at random during the experimental session. The total score from the Buss-Durkee Hostility Inventory was significantly increased after testosterone. This was due solely to increases in the Physical Aggression Subscale. In addition, testosterone signilicantly increased the number and rate of aggressive responses compared to placebo treatment and baseline. These testosterone-induced increases in aggressive responding were not due to non-specific stimulant effects since non-aggressive responding was unaffected. This is the first demonstration of testosterone-induced aggressive responding in a controlled laboratory study in which the dose was controlled by the investigator.

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DRUGS, IMMUNE RESPONSE, HIV AND OTHER INFECTIOUS DISEASES: A REVIEW OF THE SOCIO-EPIDEMIOLOGICAL LITERATURE

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A critical review of the socio-epidemiological literature was conducted to examine the hypothesis that the effects of drug or alcohol on the immune system might accelerate susceptibility or progression of HIV and other infectious diseases. Published studies were identified through searches on MIDLINE, AIDSLINE, and other bibliographic databases and reviewed for their study design features, including populations and N's, measures of drug use, immune response, infectivity, study findings, and strengths/limitations. Our review suggests that the majority of studies to date have found limited and small associations between alcohol/drug measures and progression of HIV. However, results may be confounded by design features including studies that examine risk groups rather than drugs, limited dose response variations in measures of drug use, and cause-effect relationships (unknown dates of infections). Interpretation of results is made especially difficult due to the confounding effects of polydrug use. Future studies need to address these present shortcomings and take advantage of multiple disciplinary approaches. A multi-disciplinary team of CPDD scientists are addressing these issues.

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COMORBIDITY IN DRUG ABUSER POPULATIONS: RESEARCH REVIEW/COMMENTARY

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Research has suggested that comorbidity, the concurrence of substance abuse disorders with other psychiatric disorders, may have prognostic value and important implications for the treatment of substance abuse. Knowledge of the prevalence of comorbid disorder is important because it will enable treatment services to be appropriately configured and designed for clinical drug treatment populations. The form and duration of comorbidity may be influenced by a variety of factors which include the class of drug being abused, the duration of drug use, individual sensitivity to drug effects and whether the drug effects are acute, or due to withdrawal or residual conditions. This review will address three important scientific questions. 1) What is the prevalence of comorbid disorders in a drug abuser population? 2) What is the stability of psychiatric diagnoses in a drug abuser population? 3) Does the existence of a comorbid disorder influence the outcome of drug abuse treatment? Comorbidity in drug abuser populations is described as the five "A's" (*e.g.,* affective disorder, anxiety disorder, anti-personality disorder, AIDS, and attention deficit disorder).

DRUG TREATMENT CAREERS: SHORT, LONG, AND INDEFINITE

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The UCLA Drug Abuse Research Center has been conducting studies to improve the scientific and clinical understanding of individual drug treatment careers and related health care delivery issues. Data are being collected from various sources to include subjects representing a wide range of drug use patterns and having diverse histories of treatment experiences. We examine closely each episode of treatment and the cumulative effects of sequential episodes. Additional measures include readiness and motivation for treatment, treatment history and outcome, other critical life history events, and various HIV-risk behaviors. Analyses will be conducted to address the relationships among drug use, readiness and motivation, treatment utilization, and outcomes. Special contrasts will be made between career patterns (*e.g.,* those in an early stage of a treatment career versus those with longer treatment histories), and users who have ceased drug use versus those who continued use into late ages.

TECHNOLOGICAL ADVANCES IN DATA COLLECTION

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Paper and pencil methods of data collection involve a series of standardized steps: the interview, data checking for inconsistencies, data tracking and transfer, data entry, data re-entry, data corrections, and data storage. These steps have been necessary to ensure data integrity and accuracy, but this process is time consuming and costly. Therefore, we designed a data collection method using a pen based computer, which allows interviewers to enter data directly into the computer during the interview. Data is screened for errors by the computer and then downloaded for analysis, thus eliminating the steps of data entry, re-entry and corrections, and simplifying data checking, transfer and storage. The objective of this research was to answer three questions: 1) Is the pen based Addiction Severity Index (ASI) a legitimate method lo assess patients within clinical and research contexts? 2) Does the pen based ASI provide a more accurate means of collecting data? 3) Is the pen based ASI more cost effective then the standard paper and pencil method of data collection and entry? The preliminary data from the study found no problems with conducting an ASI interview using the pen based system. Clients reported no concerns regarding confidentiality or intimidation, and the pen based ASI was accepted by interviewers and clients. There was consistency in the responses for both data collection techniques, as well as no differences in the time to complete the assessment, nor the quality of the interviews. The pen based ASI checking method was found lo reduce more errors than the conventional method of human data checking, virtually eliminating all composite score item errors. Finally, using data from a recently completed study, we designed a hypothetical cost-benefit analysis of both methods of data collection. Costs were based on an hourly salary of $14.00. The rate per case for completing and entering the standard ASI was $20.24, and $14.03 per case for the pen based ASI. Thus, the pen system of data collection yielded a 31% reduction in cost. The findings of this study support the use of pen systems for data collection.

A META-ANALYSIS OF PSYCHOMOTOR, SUBJECT-, AND STAFF-RATED EFFECTS IN ABUSE LIABILITY STUDIES OF ANXIOLYTICS

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Power analysis is crucial to the planning and design of efficient and effective studies. Information on effect sizes derived from meta-analysis can be used lo provide good estimates of power for future research. The present meta-analysis examined the statistical power of 13 techniques for the statistical analysis of time course data. Six studies of abuse liability of anxiolytics and related sedative compounds were examined. A range of measures was chosen for the meta-analysis including subject and observer ratings of subjects' responses to drug and measures of psychomotor performance. Data were analyzed by a number of different techniques including raw score and change from baseline time course analyses (TC), peak response (PEAK) calculated four different ways, area under the time course curve (AUC) calculated 3 ways, time to peak, slope (linear and quadratic), and variance. A meta-analysis was conducted comparing the effect sizes across measures of response to drug and techniques of analysis. Effect sizes for measures of psychomotor performance and staff ratings were significantly higher for AUC and TC methods (1.05 - 1.09) than for PEAK methods. Effect sizes for subject-rated measures were significantly smaller and there were no significant differences among the types of analyses for these measures, although there was a trend for peak analyses to be more powerful. The robustness of effect sizes in these small N (9-14 subjects) studies demonstrates the efficiency and power of repeated measures designs. The average effect sizes calculated in this meta-analysis can be used in the planning of future abuse liability studies of psychotropic drugs.

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SMS: A SOFTWARE STRATEGY FOR ACUTE EFFECTS STUDIES

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Acute drug effect studies may employ a variety of subjective and objective measures. Both the data volume and some measures' critical liming often require the data lo be entered directly into a laboratory computer. While stand alone software exists for many families of measures, it can be difficult to automate the integration of these measures into a single, rapidly executed framework for task control and data management. The alternative, developing all software locally to a consistent standard, requires an appropriate organizing strategy.

Our approach for human studies is called SMS, the Scheduled Measurement System, and it facilitates rapid program development, uniform data management across measures, and immediate post-experiment analysis. Straightforward questionnaires of discrete choices and visual analog scales, optionally including summary scales accumulated across questions, can be created about as fast as their text can be typed. For more complex measures, such as EEG or DSST, libraries of data management and user interface functions shorten the development cycle. A single daily printed report for each subject includes all of the measures, with selected variables graphed against elapsed time since drug administration. After an experiment, its data can be exported along with an associated SAS program defining all variables and formats.

Rapid cycling among diverse measures is critical to some research paradigms. In a recent study comparing IV remifentanil and fentanyl, an abbreviated subset of measures was scheduled at one and three minutes post infusion, while the complete measure battery was scheduled only al later limes post infusion. The abbreviated subset captured some peak effect similarities that were no longer evident at the later times.

DEVELOPMENT OF A MULTIMEDIA CLASSROOM PRESENTATION ON DRUG ABUSE

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It is now possible with modestly priced computer equipment and simplified software to prepare multimedia classroom presentations. This format allows for the incorporation of bullet charts, graphs, animation, laboratory simulation, and audio/video material. Such a design not only enlivens presentations but brings in several types of format not previously possible. The hardware included a Macintosh 840AV 16/1000 with a Radius VideoVision Studio board and a Sony SVHS-VCR. ASTOUND^{TM}, presentation software, was used to create bullet charts, generate narration, edit sound/video, and incorporate graphic material produced by other software. Less than four hours of software orientation were necessary lo generate fairly sophisticated slides. The resulting 44-slide presentation included a musical attention-getting device for the audience, animated bullet charts and graphs, and video-clips showing studies on reward centers in rats, deep electrode studies in humans and the origin of heroin. This presentation was well-received by our second-year medical class and at a national workshop on pharmacology teaching (Assn. for Med. Sch. Phcl., 1994). For faculty, this provides exciting new approaches to teaching, the inclusion of a broader range of materials, better ways to explain thoughts and ideas, the channeling of creative energies into new areas, and the ability to make alterations in the final product at any time prior to presentation. For students who have a mind-set for receiving information via such technology, it makes our teaching consistent with their expectations.

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CHRONIC EXPOSURE TO MORPHINE ATTENUATES LEUKOCYTE-ENDOTHELIAL INTERACTIONS (LEI) IN THE RAT MESENTERY

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The profile of LEI is a critical indicator of a functional immune system. The effects of chronic treatment with morphine on LEI were studied in the rat mesentery. Adult male Harlan Sprague-Dawley rats were assigned to receive two pellets of either morphine sulfate (75 mg /pellet) or placebo on Day 1 and four pellets on Day 2. This regimen has been shown to induce a high degree of opiate tolerance and dependence. On Day 5, intravital microscopy was used to evaluate microvascular hemodynamics in mesenteric venules, including leukocyte-endothelial adhesion (LEA) and rolling white blood cell (WBC) flux during basal and inflammatory conditions. Inflammation was induced by topical suffusion with the chemotactic agent FMLP (10^{-7} M). The rolling WBC flux of morphine animals was significantly lower than that of placebo animals during both basal and inflammatory conditions, suggesting reduced total WBC. The LEA response to FMLP of morphine animals was significantly lower than that of placebo animals during inflammatory, but not basal conditions. Chronic exposure to morphine also decreases expression of intercellular adhesion molecule-l (ICAM-1) in the mesentery determined by RT-PCR. Attenuation of LEI reveals an *in vivo* immunosuppressive condition following chronic exposure to morphine. The attenuation of these immune events at both cellular and molecular events may be important mechanisms underlying immunosuppression seen in morphine addicts.

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THE FREQUENCY OF EXPOSURE TO MORPHINE DIFFERENTIALLY AFFECTS CTL ACTIVITY IN ALLOIMMUNIZED MICE

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Previous results show that chronic exposure to morphine (50 mg/kg, s.c. daily) over 11 days in alloimmunized C3H/HeN mice suppresses cytotoxic T lymphocyte (CTL) activity of splenic lymphocytes (SL) and peritoneal lymphocytes (PL). To further determine the time-dependency of this observation, alloimmunized (with 1 X 10^7 C57BL/6 SL) C3H/HeN mice were exposed either acutely (one time two hours prior to alloimmunization) or subchronically (daily over a 120 hr time period) with morphine (50 mg/kg, s.c.). Five days following alloimmunization, the mice were sacrificed and SL and PL were assessed for CTL activity using EL-4 lymphoma cells (H-2^b). Whereas subchronic exposure to morphine had no effect on PL or SL CTL activity, acute morphine exposure significantly suppressed PL CTL activity. Specifically, PLs from vehicle-treated mice displayed 44.8±7.0 lytic units (LU) compared to 20.0±6.0 LU from PLs of acute morphine-treated mice. Pretreatment with naltrexone completely blocked the morphine-mediated suppression implicating the involvement of opioid receptors. Column depletion chromatography identified the PL CTLs to be both $CD4^+CD8^-$ and $CD4^-CD8^+$. Morphine (10^5 -10^{11} M) added to one-way mixed lymphocyte cultures, (C3H/HeN X C57BU6 SL) had no effect on the generation of CTLs. Collectively, the administration of morphine induces a tim/e-dependent suppression of CTL activity in alloimmunized mice through an indirect rather than direct manner.

MOLECULAR ANALYSIS OF OPIOID RECEPTOR EXPRESSION IN IMMUNE CELLS

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Opioid peptides and opioid alcaloids have been shown to modulate several immune responses such as natural killer cell activity, antibody production, lymphocyte proliferation, and macrophage activity. Experimental results of opioid binding in immune cells appears controversial. The cloning of the opioid receptor cDNAs has enabled us to generate specific probes to assess the presence of opioid receptors on cells of the immune system. Several groups including our laboratory have detected mu, delta, kappa, and a opioid receptor-like(ORL) mRNA in human peripheral blood mononuclear cells by RT-PCR. Restriction analysis of these PCR products yields the pattern expected for the human neuronal-derived opioid and ORL receptors. In addition, we have identified Ihe expression of opioid receptor mRNA by *in situ* hybridization analysis in tissue sections from lymph nodes. With cRNA probes to the mu, delta and kappa and the ORL receptors we found a specific labeling in scattered immune cells. Immunohistochemical studies using lymphopoietic markers in adjacent lymph node sections suggest that opioid receptor mRNA may be expressed in a population of T or B cells outside the germinal centers.

Furthermore additional evidence of the ORL receptor mRNA expression in the human immune system has been confirmed by Northern analysis of multiple types of immune tissue. These studies provide additional evidence for the proposed opioidergic modulation of the human immune system. Further studies are in progress to assess the opioid receptor expression in the different kind of immune cells.

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KAPPA OPIOID RECEPTORS IN HUMAN MICROGLIA: SUPPRESSION OF HIV-1 REPLICATION

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Kappa opioid peptides have been postulated to modulate immune responses within the brain. We investigated the expression of kappa opioid receptors in microglia, resident macrophages of the brain. Using a primer set encoding for human kappa opioid receptor gene and reverse transcription-polymerase chain reaction (PCR) analysis, we found that kappa opioid receptor mRNA was constitutively expressed in primary human fetal microglial cells. Sequencing analysis revealed 99% homology in the PCR product of 388 bp with the parent gene sequence. To verify binding on the cellular level, we found that a fluorescein-labeled U50,488-like compound, a kappa opioid receptor selective ligand, bound lo the microglial cell surface when anti-fluorescein R-phycoerythrin-conjugated antibody was used (75% cells were positive versus 9% in control cultures). The effect of U50,488 on HIV-1 replication was studied in acutely infected microglial cells, the primary site of HIV-1 replication within the CNS. U50,488 markedly suppressed HIV-1 replication with a bell-shaped dose response relationship. Maximal inhibition (decrease by 54%) was observed at a concentration of 1 pM. The anti-viral effect of U50,488 was completely blocked by treatment with nor-BNI, suggesting a kappa opioid receptor-mediated mechanism. These findings suggest that microglial cells constitutively express kappa opioid receptors which, when activated, interfere with HIV-1 replication.

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HEPATITIS B VACCINATION OF METHADONE MAINTAINED PATIENTS: A PILOT STUDY

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The major diseases affecting heroin addicts are human immumodeficiency virus (HIV-1), tuberculosis, hepatitis B (MB), hepatitis C, with delta hepatitis an additional risk to patients infected with HB. Until recently, >80% of all heroin addicts were serologically positive for HB. HB vaccination has not been offered to this population due to questions regarding both its effectiveness and patient compliance. Recently, 74% of patients admitted to two urban methadone programs over a 14 month period since 1993 were negative for HB surface and HB core antibodies (anti-HBs and anti-HBc) and HBs antigen (Ag), demonstrating a marked increase in the percentage of patients not yet exposed to HB infection, most likely due to AIDS risk-reduction education. These patients therefore need HB vaccination for protection in possible future exposures. Method: To study efficacy of HB vaccination, we measured immune response to HB vaccine in 41 former heroin addicts entering or already in methadone maintenance treatment. After screening for HB markers to rule out pre-existing infection and immunity, subjects were vaccinated according to standard medical procedure with three doses of intramuscular vaccine (RECOMBIVAX HB®) at 0, 1, and 6 months. Antibody response was assessed at 0, 1, 6, and 12 months by measuring anti-HBs titers using a commercial immunoassay kit (Abbott) along with other measures including HIV-1 status. Results: Eighty-five percent (35/41) patients complied with the protocol, with 17 completed to date. Seventy-six percent of the anti-HIV-1 seronegative subjects showed a protective level of response to the vaccine (anti-HBs ratio $\geq$10) by the 12 month assay. Two subjects were anti-HIV-1 seropositive: one with a CD4 count of 284/µl did not develop an adequate immuneresponse; the other was protected by six months (anti-HBs ratio = 13). HB vaccination, needed by many methadone maintained patients, is both feasible and effective.

ACKNOWLEDGEMENTS: NIDA P50-DA05130, DA00049; NIH MO1-RR-00102; the generous gift of vaccine by Merck & Co..

DETERMINATION OF HEPATITIS C CARRIER PREVALENCE IN HEROIN ADDICTS BY POLYMERASE CHAIN REACTION ANALYSIS: CORRELATION WITH LIVER FUNCTION ABNORMALITIES

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Hepatitis C virus (HCV) infection is highly prevalent in intravenous heroin addicts. Antibody studies show that over 80 to 90% of addicts have been exposed to HCV. Since chronic HCV infection is contagious and may lead to cirrhosis, liver failure, and carcinoma of the liver, it is essential to know the actual carrier prevalence and whether the presence of abnormal liver function studies commonly observed in addicts is likely a result of HCV infection. To help answer these questions, 61 intravenous heroin addicts in outpatient methadone treatment were tested for the presence of HCV antibodies by recombinant immunoblot assay (RIBA). Fifty-five (55) of the 61 (90.2%) subjects tested positive. Forty-seven (47) of these subjects were tested for the presence of HCV RNA in serum or lymphocytes by polymerase chain reaction (PCR). This assay presumably detects actual virus RNA and the presence of a carrier state. Serum assays were also done for aspartate aminotransferase (AST), alaninine aminotransferase (ALT), total bilirubin, albumin, globulin, A/G ratio, and total protein. Of those tested by PCR, 33 (70.2%) showed detectable HCV RNA in serum or lymphocytes. Elevated AST and ALT levels were found in 60.6% and 54.5% respectively in PCR-positive subjects compared to 7.7% and 0% in negative subjects ($P<.05$). Abnormal serum protein concentrations were found in 42.4% of PCR-positive compared to 23.1% of PCR-negative subjects. Data collected here suggest that about 70% of intravenous heroin addicts are hepatitis C carriers, and liver enzyme elevations in addicts are primarily produced by persistent HCV infection. Protein abnormalities appear to be less consistently associated with persistent HCV infection.

ALVEOLAR MACROPHAGES DERIVED FROM THE LUNGS OF TOBACCO, MARIJUANA AND COCAINE USERS ARE COMPROMISED FUNCTIONALLY

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Previous studies indicate that both tobacco (T) and marijuana (M) may differentially compromise pulmonary host defense. However, the specific functional defects still remain incompletely characterized. In this study we address alterations in immune function as mediated by lung alveolar macrophages (AM) lavaged from smokers of T, M and cocaine (C). AM are the lung's resident phagocytic defense against bacteria and fungi. Therefore, we have characterized AM phagocytosis and intracellular killing of both fungal (Candida pseudotropicahs) and bacterial (Staphylococcus aureus) organisms and correlated these functional activities with cyotkine profiles. Subject groups included smokers of T, M, or C alone, as well as combination subject groups (T/M, T/C, M/C and T/M/C). M and C, alone or in combination with other substances, significantly ($p<0.05$) reduced the anti-candida activity of AM when compared to AM from tobacco smokers or normal controls. This is not reflected in an impaired ability to ingest C. pseudotropicalis so the specific functional defect is in killing and degradation of ingested organisms. Anti-staphyloccus activity was within the control range for T smokers and only slightly impaired for M or T/M smokers. However, M/C and T/M/C smokers were characterized by a 50-70% decrease in bactericidal activity (when compared to AM lavaged from normal controls) and this defect was most pronounced in C-only smokers (<40% of normal killing). Phagocytosis of bacteria remained normal in all subject groups confining anti-bacterial functional impairment to killing of ingested organisms. Interestingly cytokine profiles indicated that AM from M subjects appear to secrete less of most cytokines, but AM from C subjects produced the lowest cytokine levels, correlating decreased cytokine production to immune impairment in users of marijuana and cocaine.

HEMATOPOIETIC EFFECTS OF SUBCHRONIC EXPOSURE TO INHALED ISOBUTYL NITRITE

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Abuse of nitrite inhalants is widely practiced by male homosexuals and may be a risk factor for HIV infection or Kaposi's sarcoma. We have reported that mice exposed to inhaled isobutyl nitrite for 45 minutes/day for 14 days had severe decrements in three major immune mechanisms; T-dependent antibody induction, specific T cell mediated cytotoxicity, and macrophage mediated tumoricidal activity. A single 45 minute exposure to the inhalant decreased counts of peripheral blood erythrocytes by 7% and leukocytes by 42%. We now report that after 14 daily exposures to 900 ppm isobutyl nitrite, peripheral erythrocyte counts were elevated by 7%. Consistent with this, bone marrow and spleen erythroid progenitor cells (BFU-E) were more than doubled, as were peripheral blood reticulocyte counts. On the other hand, subchronic exposure to the inhalant reduced peripheral blood leukocyte counts by 32% and similarly depressed bone marrow and splenic myeloid progenitor cells (CFU-GM). Thus, repeated destruction of blood cells appeared 10 stimulate erythroid progenitor cell activity at the expense of myeloid cells. Peripheral blood leukocytes were probably replenished from the spleen, rather than with new cells from the bone marrow.

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MORPHINE PELLETS INDUCE SEPSIS IN MICE

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Studies from our laboratory have shown that subcutaneous implantation of 75 mg morphine pellets in mice is immunosuppressive. In the course of these studies, we observed that some animals die from morphine pellet implantation. Recently, we observed that when peritoneal macrophages were pooled and cultured in antibiotic-free medium, the cells from morphine-pelleted C57BL/6J mice, but not placebo-, naltrexone (NTX)-, or morphine + NTX-pelleted mice, were contaminated with Proteus mirabilis and Escherichia coli. To examine the possibility that morphine was sensitizing to endogenous Gram-negative infection, livers of morphine-pelleted mice and appropriate controls were removed, homogenized and plated on bacteriologic medium 24 hours after pellet implantation. P. mirabilis and E. coli were cultured from 75% of morphine-pelleted mice. Simultaneous implantalion of a NTX pellet reduced the incidence of bacterial colonization to 42%. The numbers of organisms per plate in animals receiving morphine + NTX were also significantly reduced. The livers of mice receiving NTX pellets alone had no bacteria, while single colonies of E. coli were cultured from 25% of livers from placebo-pelleted mice. Similar results were obtained when C3HeB/FeJ mice were implanted with morphine pellets, although the time for maximal colonization occurred 48 hours after pellet implantation. Thus, morphine pellet implantation appears to induce escape of Gram-negative organisms from the gut. In addition, morphine pellets sensitized mice to subsequent challenge with a sublethal dose of endotoxin. These studies raise the possibility that morphine may sensitize patients to Gram-negative sepsis and subsequent endotoxic shock.

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REGIONAL BRAIN BLOOD FLOW DURING CUE-INDUCED COCAINE CRAVING

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Human cocaine users often experience profound arousal and drug desire when they encounter cues (people, places, paraphernalia, etc.) associated with cocaine. The brain substrates of cue-induced craving are not yet known, but pre-clinical research has demonstrated that cues which signal cocaine or other natural awards can produce increased dopamine release in mesolimbic brain regions. Increased mesolimbic activity should be reflected in regional cerebral blood flow (rCBF) patterns, as rCBF mirrors brain synaptic activity. We expect increased limbic rCBF in patients experiencing cue-induced craving. In an ongoing study, rCBF was imaged in abstinent cocaine patients (n=9) and matched controls without a cocaine use history (n=5). The single imaging session featured 1) ambient room stimuli (resting baseline), 2) non-drug videos, and 3) cocaine-related videos which reliably induce craving. Imaging of rCBF was accomplished with PET (Positron Emission Tomography) scans, using radioactively-labeled (O-15) water as the flow tracer. PET scans for each subject were c&registered with an MRI (magnetic resonance image) to permit anatomical localization of radioactivity. Consistent with the hypothesis of limbic activation to cocaine cues, several cocaine patients showed rCBF increases in amygdala and temporal pole during the cocaine video (as compared to resting baseline). Systematic activation did not occur in non-limbic comparison regions, nor in response to the non-drug cues. Control subjects generally did not show rCBF increases to either video type. If this pattern of results proves reliable, it suggests limbic activation may be one component of cue-induced craving.

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DIFFERENTIAL CEREBRAL BLOOD FLOW EFFECTS CAUSED BY MU VERSUS KAPPA OPIOID AGONISTS

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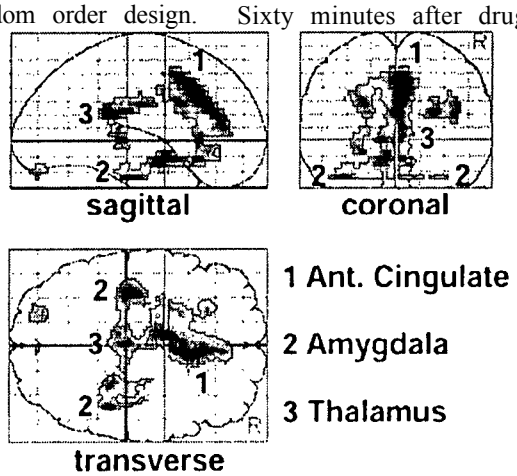
Humans experience the subjective effects of mu versus kappa opioid agonists differently. The purpose of this study was to test the hypothesis that opioids with either mu or kappa effects would produce anatomically distinct patterns of cerebral perfusion as assessed with Single Photon Emission Computed Tomography (SPECT). Non-dependent opioid abusers (n = 9) received intramuscular injections of 4 mg/70 kg hydromorphone (a prototypic mu agonist), 6 mg/70 kg butorphanol (a mixed agonist-antagonist with kappa opioid effects), and saline placebo in a double-blind, random order design. Sixty minutes after drug administration the SPECT tracer [^{99m}Tc]-HMPAO was given intravenously. SPECT scans were performed using a triple head, high resolution camera. Analyses were done using a modified statistical parametric mapping (SPM) method. Hydromorphone lead to a significant increase in regional cerebral blood flow (rCBF) in three regions belonging to the limbic system (see figure to the right), while butorphanol caused a mixed picture of distributed increases and decreases in rCBF. These results suggest that opioids known to have different patterns of subjective and behavioral effects also produce anatomically distinct patterns of change in regional cerebral blood flow. In addition, this study demonstrates the application of SPECT functional neuroimaging in the study of medications with abuse liability.



EFFECTS OF NALMEFENE ON D_1 AND D_2 DOPAMINE RECEPTORS IN RAT BRAIN AS MEASURED BY PET

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The interaction between central opioid and dopaminergic systems has been the focus of much attention due to their interactive role in reinforcement and locomotor activity. The present study investigated the effects of acute and chronic administration of nalmefene, an opioid antagonist with μ and κ receptor selectivity, on the binding potential for [^{11}C]-SCH23390 and [^{11}C]-N-methylspiperone at D_1 and D_2 dopamine receptors respectively, using positron emission tomography (PET). Adult male Sprague-Dawley rats received either a single injection of 10 mg/kg of nalmefene or control vehicle solution one hour prior to the PET scan (acute) or 10 mg/kg/day of nalmefene or vehicle for seven days via a subcutaneously implanted osmotic minipump (chronic). Following acute administration of nalmefene, a significant increase in the binding potential of [^{11}C]-SCH23390 in the striatum was found, whereas a significanl decrease was found in the olfactory bulb. No changes in [^{11}C]-N-methylspiperone binding were found. Following chronic nalmefene administration, no significant changes in either [^{11}C]-SCH23390 or [^{11}C]-N-methylspiperone binding were detected. These results suggest that nalmefene administration produces transient changes in the binding potential of D_1 receptors that are normalized after one week of steady-state administration.

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ALTROPANE: A NOVEL SPECT IMAGING AGENT FOR COCAINE BINDING SITES ON THE DOPAMINE TRANSPORTER

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The dopamine transporter is a principal target of cocaine in the brain. Brain imaging may be used to monitor changes in the transporter of cocaine abusers and to evaluate transporter occupancy of potential cocaine therapeutic agents (Madras, *et. al.,* 1994). The present study highlights a novel SPECT imaging agent (single photon emission computerized tomography) that displays favorable characteristics for these applications. In vitro, [^{125}I]altropane has high affinity for the dopamine transporter in human striatum (Kd: 4.96 ± 0.38 nM, Bmax: 212 ± 41.1 pmol/g, n=4) and a pharmacological profile consistent with binding to the dopamine transporter. It is approximately 28-fold selective for the dopamine over the serotonin transporter. In monkey brains, it distributes *in vitro* and *ex vivo* almost exclusively to brain regions rich in dopamine. SPECT imaging reveals high uptake in monkey striatum within 30 minutes (striatum:cerebellum ratio > 10). Binding is reversible and rapidly reduced by WIN 35,428, an inhibitor of dopamine transport, but not by citalopram, an inhibitor of serotonin transport. These studies highlight the favorable properties of [^{123}I]altropane as a SPECT imaging agent for the dopamine transporter in brain (high affinity and selectivity for the dopamine transporter, rapid and reversible accumulation in dopamine regions of the brain) and the suitability of the drug for cocaine abuse research.

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DETECTION OF ABNORMAL CEREBRAL METABOLISM IN POLYDRUG ABUSERS DURING DETOXIFICATION USING ^{31}P MR SPECTROSCOPY

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Phosphorus magnetic resonance spectroscopy (^{31}P MRS) was performed on 10 neurologically normal/HIV-seronegative inpatient polydrug abusing men aged 34 ± 6 years meeting DSM-III-R criteria for concurrent cocaine and heroin dependence (self-reported current/chronic cocaine and heroin use averaged 6 g/week and 11 "bags"/day, respectively, and 7 and 12 years, respectively) and 11 controls aged 32 ± 8 years. The ISIS volume localized spectroscopy technique (Tip angle 90°, TR=3 sec, TF=1 msec, 64 averages) was utilized to obtain phosphorus signals at 1.5 Tesla from a 5 cm thick axial brain slice paralleling the orbitomeatal line and passing through orbitofrontal/occipital cortices. Polydrug abusers were scanned two to seven days after admission, during methadone detoxification (average study day dose 19 mg, administered seven hours prior to scanning). High energy phosphorus and phospholipid metabolite levels were calculated as molar percent values after determining that total phosphorus levels were equivalent in both groups. Elevated phosphomonoester (PME) levels and decreased nucleoside triphosphate (both ß-NTP (ATP) and total NTP) levels were detected in polydrug abusers, suggestive both of membrane and bioenergetic dysfunction. These alterations did not correlate with study day methadone dose, number of days of abstinence, or self-reported alcohol/tobacco use. PCr levels were inversely correlated with current cocaine use. ß-NTP levels were positively correlated with years of heroin use. These dam suggest that cerebral high energy phosphate and phospholipid alterations which are likely to be the result of chronic long-term heavy drug abuse and/or withdrawal are detectable with ^{31}P MRS in polydrug abusing men.

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REGIONAL CEREBRAL VOLUMES AND ASYMMETRIES IN POLYDRUG ABUSERS: A VOLUMETRIC MAGNETIC RESONANCE IMAGING STUDY

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While differences in cerebral glucose metabolism and blood flow have been related to drug abuse (DA), little is known of cerebral structural abnormalities associated with DA. Such abnormalities could reflect neurotoxicological consequences or could pre-date DA. To test whether DA is associated with structural abnormalities in brain, high resolution volumetric magnetic resonance imaging (MRI) was used to assess cerebral morphology and asymmetries in 37 polysubstance abusers and 13 controls without histories of DA. Substance abusers were segregated into groups depending upon the length of abstinence from alcohol and illicit drugs prior to MRI data acquisition. Those who were abstinent > two week constituted Group I; those abstinent < two week formed Group II. Image processing was performed with the ANALYZE© program on reformatted data sets to overcome the problems of tilt and/or rotation during data acquisition. Two investigators who were blinded to the histories of the subjects segmented the brain images by a semi-automated method; and each brain was partitioned into 20 portions using internal landmarks (anterior boundaries of genu of corpus callosum, anterior and posterior commissures, posterior boundaries of splenium) using a clip volume algorithm. Data from right-handed subjects indicated that the relative volume in the inferior prefrontal portion was smaller in DA Group I than in controls, suggesting a structural abnormality in the orbitofrontal lobe, in which abnormal glucose metabolism was seen in substance abusers. Asymmetries in controls and DA Group I resembled those previously seen in the normal population, but asymmetries were reduced or absent in DA Group II. The loss of asymmetry tended to return to control as the length of abstinence increased. Therefore, the abnormal cerebral asymmetries in DA Group II indicate reversible effects of DA on cerebral structure.

INCREASED MU-OPIOID RECEPTORS IN COCAINE ADDICTS DEMONSTRATED BY PET: ASSOCIATION WITH CRAVING

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Cocaine interactions with CNS opioid systems have been described in animals, but not yet directly demonstrated in humans. We scanned ten cocaine-dependent (DSM-IIIR) men (mean [SD] age 32 [±4] years) and seven age- and sex-matched controls with a GE4096 PET camera (FWHM resolution 7 mm) after 20 mCi of iv [C-11]carfentanil, a specific mu-opioid ligand. Cocaine addicts were studied one to four days after last cocaine use and again after four weeks of monitored abstinence on a closed research ward. Specific [C-11]carfentanil binding was significantly increased (25-52%) in caudate, thalamus, and neocortical regions of the cocaine addicts vs. healthy controls. Self-rated cocaine craving during the week before and just prior to the first PET scan was significantly correlated with mu-opioid binding in amygdala, anterior cingulate, frontal, and temporal cortex. Mu-opioid binding in (caudate and thalamus only) was significantly negatively correlated with urine benzoylecgonine concentration prior to the first PET scan, but not with self-reported cocaine use over the prior week, month or three months. The increase in [C-11]cafrentanil binding persisted after four weeks of cocaine abstinence in six of nine subjects. These results suggest that chronic cocaine abuse is associated with upregualtion of mu-opioid receptors in specific brain regions, which correlates with intensity of cocaine craving.

OPTIMIZING THE PREDICTION OF RETENTION IN METHADONE MAINTENANCE TREATMENT

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A study of retention in two outpatient methadone maintenance clinics was completed. Although they differed in retention rates and urinalysis results, similar factors in each clinic predicted retention. Accordingly, the clinic data were combined for this purpose. Separate analyses were completed al admission for all MM clients (N=734) and at two weeks post-admission for clients who remained 14 or more days (N=672). Proportional hazards regression models were developed for each sample. At admission, a model consisting of six pre-admission variables alone was developed. Included were age, confinement during the past 12 months, alcohol use at least weekly, time in jail as an adult, weeks of employment in the past 12 months and weeks of previous methadone maintenance treatment. At two weeks, models with only pre-admission and pre-admission plus in-treatment variables were compared. Pre-admission variables alone were highly significant in predicting retention in both models. However, in the two week model, the addition of cocaine urinalysis results significantly improved the prediction over pre-admission factors alone. In classifying subjects into four groups based on their predicted retention (hazard) scores, the admission and full two week models yielded comparably good results. Thus, while pre-treatment indicators may be optimal for predicting retention at admission, in-treatment variables may enhance prediction at two weeks post-admission.

MODEL TREATMENT RESEARCH UNIT PATTERNED AFTER A VERY EFFECTIVE TREATMENT FACILITY IN U.S.A.

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We have hypothesized that the model of treatment-research clinic for heroin addiction, which is linked to an academic medical center, and which uses methadone pharmacotherapy in conjunction with the overall management treatment, can be replicated in a different culture, where addicts entered treatment for both similar and different problems, with resultant similar and effective outcomes. Following earlier experience at a very effective methadone treatment facility in the USA, we established a model methadone maintenance treatment and research unit in a major hospital in Tel Aviv, Israel. Addiction, as well as methadone treatment, were insufficiently taken care of in Israel, and efforts were done by us to pattern our unit after the most effective treatment clinic in the U.S. as well as to give the message that narcotic addiction is a disease. In the 18 months since the clinic opened, 96 people underwent initial testing, 12 of whom were not accepted to treatment. Eighty-four patients received at least one dose of methadone (1 day - 16 months). Our methadone dose range is 20-150 mg (mean 94 mg) and our age range 22-54 (mean 38). After 12 months in treatment, 15% the of patients had three or more positive urine for opiates. Of the 84, 28 left treatment: 19 voluntarily (four after detoxification) and nine involuntarily [imprisonment (2), violence and drug dealing (4) and continuous drug abuse (3)]. Our retention rate after 18 months is 67%. Seventy-eight of the 84 patients were tested for HIV-1, of whom one was positive. Twenty-nine patients were retested after six months of which no one had seroconversion. When we looked at changes in high risk behavior, we found significant improvement in injecting habits as well as sexual practices. Our hypotheses is supported and the methadone maintenance treatment-research model from New York City has been successfully replicated in Tel Aviv, Israel.

LEVOMETHADYL ACETATE (LAAM): INTRODUCTION INTO EUROPE

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Levomethadyl Acetate (LAAM), a long-acting synthetic opiate, was approved by the FDA for treating opioid dependence in July, 1993. In May, 1994, two clinics in Portugal, the Centro das Taipas in Lisbon and the Centro da Boavista in Oporto, were approved by the Ministry of Health for outpatient LAAM trials. Patients and staff at the Taipas Clinic had no prior experience with methadone maintenance, but had extensive experience in drug-free treatment and the use of the narcotic antagonist naltrexone. Patients selected for treatment with LAAM had failed three prior drug-free or naltrexone treatments. Because they had a relatively low level of physical dependence, stabilization was initiated with low doses of LAAM which were gradually increased to the 40-60 mg, three times per week range. Several patients treated previously with naltrexone were not able to tolerate the transition to LAAM. They complained of drowsiness, headache, and nausea. In Oporto, where the Boavista Clinic has 900 methadone patients, a separate LAAM clinic was established. Heroin. dependent patients were first stabilized on methadone for one week before crossing over to LAAM. Most tolerated the medication well and reported a marked decrease in their urge to use other opioids. Based on this early experience, LAAM appears to be well accepted.

LAAM INDUCTION AND RETENTION IN CLINICAL PRACTICE

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Evergreen Treatment Services was one of the first programs approved for the clinical use of levo-alpha-acetylmethadol (LAAM) in the U.S., introducing the drug as an alternative treatment approach in February, 1994. Clinical protocols were developed, staff training occurred and the program was made available to all patients, except pregnant or nursing women, in methadone treatment who had been on methadone for 30 days or longer (n=350). Consistent with previous research findings, we have struggled with retaining patients on LAAM. During the first 15 months of the program 62 patients volunteered for LAAM therapy. Of the 62 initial patients, 48 (77.4%) returned to methadone treatment during the 15 month period; those patients had a mean length of time on LAAM of 71.9 days (median=39.0, s.d.=81.6). The 14 patients who remain on LAAM have a mean length of 368.5 days (median=379.0, s.d.=61.8). Patients cite difficulties in adjusting to the 72 hour LAAM dose and unpleasant side effects of LAAM as compared to methadone as the principal reasons for returning to methadone. Medical providers have tried three separate LAAM induction strategies to address these problems. An analysis of the demographic characteristics, *i.e.,* gender, age, ethnicity, employment, marital status and education, of those who remained on LAAM versus those who returned to methadone treatment found no statistically significant differences in any of the variables examined. We also examined the length of prior methadone treatment history, sizes of LAAM 48 and 72 hour dose levels, number of medical appointments while on LAAM and the identity of the primary medical provider conducting the LAAM inductionas well as the number of positive urinalyses during the six months prior to LAAM and while on LAAM for the two groups and found no significant differences between the groups **on** any of these variables. Thus, we could find no observable patient variable which can help predict successful retention on LAAM.

ACUTE EFFECTS OF INTRAVENOUS AND ORAL LAAM IN HUMAN SUBSTANCE ABUSERS

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LAAM is a long-acting mu opioid agonist recently approved for use in opioid maintenance treatment. Previous clinical studies reported that the onset of the effects of intravenous (i.v.) LAAM was delayed up to six hours after administration, while preclinical studies suggested an immediate onset of effects. This study evaluated and compared the pharmacodynamic and pharmacokinetic profiles of i.v. and oral (p.o.) LAAM in humans. Inpatient volunteers (n=6) with opioid abuse histories participated in five experimental sessions. LAAM was administered once weekly in a constrained randomized order (*e.g.,* low dose of a route preceded the high dose) at 0 mg, 20 and 40 mg, i.v., and 20 and 40 mg, p.o., under double-blind, double-dummy conditions. Plasma samples and physiologic, subjective, and behavioral measures were collected intensively for 8.5 hours and at regular intervals for four days. Intravenous doses of LAAM produced miosis and increased ratings on subjective measures of euphoria (*i.e.,* "drug liking," "magnitude of high") within five minutes of infusion; these effects peaked at four to six hours post-administration. Pharmacokinetic studies indicated that only the parent compound, LAAM, was detected in plasma during the first 30 minute post-infusion. In contrast to the time course observed for i.v. LAAM, the pharmacodynamic effects of p.o. LAAM appeared within two. to three hours and peaked between 9-12 hours post-administration. These effects were dose-related for both routes. The magnitude of subjective effects of i.v. LAAM was greater than for the same p.o. dose, suggesting greater i.v. bioavailability. These data indicate that the effects of parenteral LAAM have an immediate onset in humans and that the use of intravenous LAAM may be associated with significant abuse liability.

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A CONTROLLED TRIAL COMPARING BUPRENORPHINE AND METHADONE MAINTENANCE

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The efficacy and safety of buprenorphine in long-term maintenance treatment were compared to methadone in 225 opiate dependent patients randomly assigned, in equal numbers, to 80 mg/day methadone (M80). 30 mg/day methadone (M30), or 8 mg/day buprenorphine. and treated in double-blind fashion for up to one year. The M80 group had significantly better retention over the first 26 weeks than the M30 ($p = .037$, Wilcoxon statistic) and buprenorphine ($p = .009$) groups. Opiate use, as measured by percent "clean" urines, was significantly different using the Kruskal-Wallis test ($H = 12.635$, 2df, $p = .002$) with M80 better than M30 ($H = 8.882$, 1df, $p = .003$) and buprenorphine ($H = 9.999$, 1 df, $p = .002$). Use of a composite outcome measure, the TES (Ling, *et. al.,* 1994), which combines aspects of retention and drug use, showed the M80 group to be superior to the M30 ($H = 10.772$, 1 df, $p = .001$) and buprenorphine ($H = 6.654$, 1 df, $p = .001$) groups. Results at 52 weeks were comparable to those at 26 weeks. The M30 and buprenorphine groups did not differ significantly on any of the above measures. No significant toxicity with 8 mg/day buprenorphine was found. These results suggest that patients maintained on 8 mg/day buprenorphine fared comparably with patients maintained on 30 mg/day methadone but neither group did as well as patients maintained on 80 mg/day methadone.

COMPARISON OF THE WITHDRAWAL SYNDROMES FOLLOWING ABRUPT TERMINATION OF BUPRENORPHINE AND METHADONE

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This study compared the physiologic and subjective withdrawal syndromes associated with abrupt cessation of buprenorphine and methadone in opiate-dependent individuals. Subjects were randomized into this double-blind, double-dummy, parallel-group inpatient study, and received either daily sublingual buprenorphine 2mg (n=7), 8mg (n=5), 12mg (n=7), or 16mg (n=8), or oral methadone 30mg (n=6) or 60mg (n=7) for 17 days followed by ten days of placebo medication. Forty subjects completed (of 55 who entered) the ten day withdrawal phase. Dependent measures included the Adjective Rating Scale (ARS), Opioid Withdrawal Scale (OWS), pupil diameter, and vital signs. Initially, a two-factor (group x day) ANOVA was used to analyze AUC scores. Mean daily data were calculated as change from baseline (identified as study day 16 and 17). Significant day effects but no group differences were observed. After finding no group differences, data were pooled for methadone (n=13) and buprenorphine (n=27) and a two-factor (drug condition x day) ANOVA was performed. This second analysis showed a significant day effect on physiologic measures, ARS and OWS. There was also a significant group x drug interaction for heart rate. The time course for subjective and physiologic measures appeared similar for both medications. Subjective measures returned to baseline levels within ten days while physiologic measures did not. These results suggest that the withdrawal syndromes following abrupt termination of buprenorphine and methadone at the doses and duration tested here may not differ and that there is a different time course for the subjective versus physiologic effects of these withdrawal syndromes. Possible medication or dose differences on onset, peak, and individual subjective withdrawal items will be evaluated.

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COCAINE USE BY OPIATE DEPENDENT HUMANS: EFFECTS OF BUPRENORPHINE OR METHADONE MAINTENANCE

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Research with non-human and human research subjects suggests that non-opiate dependent subjects self-administer less cocaine when given buprenorphine. Clinical studies with opiate-dependent cocaine abusers, however, have not consistently reported comparable effects under buprenorphine maintenance. Methadone maintained (80 mg mean dose) cocaine users, living on a hospital CRC, participated in a five week protocol. After initial stabilization on 60 mg methadone, they were divided into two groups, each tested under both 8 mg buprenorphine and 60 mg methadone. Group A was initially tested under methadone (with sublingual placebo) and Group B was gradually tapered from methadone to buprenorphine and tested first under 8 mg sublingual buprenorphine (with oral placebo). All were returned to their entry level of methadone before discharge. Testing consisted of three days of fixed dosing sessions (4 injections/day; 0, 16, 48 mg/70 kg) and three days of cocaine self-administration sessions using a choice procedure (0, 32, 48 mg/70 kg vs $5). Twenty-four-hr Holter monitoring was carried out repeatedly, cardiovascular monitoring was continuous during each session, and self-reported effects of cocaine and the opioids were measured daily, as were drug withdrawal and sleep. The transition from methadone to buprenorphine engendered moderate withdrawal symptoms which were not controlled by clonidine, but responded well to several days of oxazepam and chloral hydrate. Choice to self-administer cocaine was not differentially affected by methadone or buprenorphine. However, methadone and buprenorphine maintenance appeared to diffcrentially affect "I Want Heroin" and I want Cocaine" scores. In addition, in general, the subjective and physiological effects of cocaine were similar to those previously reported in non-opiate dependent cocaine users regardless of the maintenance medication.

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SEDATIVE ABUSE DURING BUPRENORPHINE VS METHADONE MAINTENANCE TREATMENT

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Using data from a 26 week randomized clinical trial comparing daily agonist maintenance with buprenorphine (4 mg SL, 12 mg SL) and methadone (20 mg PO, 65 mg PO), we assessed maintenance condition effects on alcohol and benzodiazepine abuse. Subjects (N=111) met DSM III-R criteria for current dependence on opioids and cocaine and were not currently dependent on benzodiazepines. Treatment groups did not differ at baseline on demographic characteristics or current alcohol or benzodiazepine use. Benzodiazepine use was assessed by weekly urine toxicology testing, alcohol by weekly self-report. Maintenance condition had no significant effect on benzodiazepine use, adjusting for weekly cocaine use, or on alcohol use, but had a significant effect on benzodiazepine use, adjusting for its use during induction, with buprenorphine 4 mg associated with highest use. Alcohol use decreased over time in all maintenance conditions. We will discuss the implications of these findings with regard to development of alternative agonist maintenance treatments.

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CHARACTERIZATION OF A NEURAL CANNABINOID RECEPTOR USING CB1 ANTISERUM

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An expression plasmid (pCORCB1-3) was constructed to contain coding sequence for a fusion protein consisting of the extracellular domain of the rat neural cannabinoid receptor (CB1) and the highly immunogenic hepatitis virus B core antigen (HBcAg-CB1). The expressed fusion protein, HBcAg-CB1, was injected into rabbits to produce hyperimmune antiserum. Laurell-rocket immunoelectrophoresis demonstrated that the fusion protein antiserum contained two subsets of antibodies, one against the external domain of CB1 and one against the Hepatitis B core antigen (HBcAg). Antifusion antibody extensively absorbed with purified HBcAg (anti-CB1 antiserum) was employed in immunofluorescence and Western immunoblotting studies to confirm its specificity to CB1. Immunofluorescence staining was observed in rat (B103) and mouse (N18TG2) neuroblastoma cells, which previously have been shown to express CB1. Western immunoblotting of analytical SDS-Polyacrylamide gels (SDS-PAGE) of B 103 and N18TG2 cell lysates displayed immunoreactive protein bands in the relative molecular weight range of 49 kDa to 65.2 kDa. Similarly, Western immunoblotting of SDS-PAGE-separated proteins from whole rat brain homogenates revealed immunoreactive bands ranging from 43.8 kDa to 66.4 kDa. These relative molecular weight ranges are in accordance with the predicted size of CB1 as extrapolated from receptor cDNA sequence. These results indicate that the polyclonal antiserum elicited against the extracellular domain of CB1 detects the neural cannabinoid receptor and may be a useful tool for further characterization of CB1 expression.

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EVIDENCE THAT THERE ARE CB1 CANNABINOID RECEPTORS IN THE GUINEA-PIG SMALL INTESTINE

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These experiments tested the hypothesis that cannabinoid-induced inhibition of electrically-evoked contractions of the myenteric plexus-longitudinal muscle preparation of guinea-pig small intestine is cannabinoid receptor-mediated. Preparations were mounted in 4 ml organ baths and stimulated supramaximally at 0.1 Hz. The cannabinoids, CP 55,940, WIN 55,212-2 and delta-9-tetrahydrocannabinol (THC), decreased the amplitude of electrically-evoked isometric contractions in a dose-related manner. Concentrations producing half-maximal inhibition were 5.3, 9.7 and 181.9 nM respectively (n=5 or 6). When injected 25 min before these agonists to yield a bath concentration of 316.2 nM, the CB1 cannabinoid receptor antagonist, SR141716A [(N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-melhyl-1H-pyrazole-3carboxamide hydrochloride], induced rightward shifts in the log concentration-response curves of CP55,940, THC and WIN 55.212-2 of 40.2, 64.9 and 32.9 fold respectively (n=5 to 8). By itself, SR141716A at concentrations of 10, 40 and 160 nM increased the twitch amplitude by 8.91 ± 3.23%, 13.03 ± 3.99% and 15.83 ± 6.65% respectively (mean ± s.e.; n=12). These increases were greater ($P < 0.05$; unpaired t test) than the change in amplitude recorded after injection of the corresponding dose of the vehicle, Tween 80 (0.11 ± 1.23%, -1.62 ± 2.63% and 0.88 ± 1.58% respectively; n=11). SR141716A (1 μM) did not reverse the inhibitory effect of 50 nM normorphine or of 200 nM clonidine. Our findings suggest that the guinea-pig small intestine contains CB1 cannabinoid receptors and, also, that it may produce cannabinoid receptor ligand(s).

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ANTAGONISM OF THE CANNABINOID CUE BY SR 141716 A SELECTIVE ANTAGONIST OF THE CB1 RECEPTOR SUBTYPE

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In animals, cannabinoids are known to induce a relevant discriminative stimulus in which the role of the central CB, receptor is not fully established. The present experiment attempts to further characterise the cannabinoid cue by using selected agonists and a selective antagonist, SR 141716 (Rinaldi-Carmona *et. al.,* 1994). Male Sprague Dawley rats (N = 18) were trained to discriminate WIN 55,212-2 (0.3 mg/kg s.c.) versus saline in Skinner boxes according to the standard protocol of drug discrimination. Learning was fast and lasted 15.7 days (11 to 23). Generalisation tests indicated that WIN 55,212-2. ^{9}-tetra-hydrocannabinol (THC) and CP 55,940 induced a cannabinoid stimulus with the respective ED_{50}s 0.032 mg/kg s.c., 0.64 mg/kg p.o. and 0.007 mg/kg s.c., SR 141716 antagonised the WIN 55,212-2 training dose (ID_{50} = 1.6 mg/kg s.c., 2.1 mg/kg p.o.) and the generalisarions to THC (ID_{50} = 0.15 mg/kg p.o.) or to CP 55,940 (ID_{50} = 0.08 mg/kg s.c.). These results strongly suggest that the cannabinoid cue is of central origin and mediated by the CB_1 receptor subtype.

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THE SYNTHESIS AND PHARMACOLOGY OF THE CANNABINOID ANTAGONIST SR141716A AND ITS ANALOGS

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The first cannabinoid antagonist SR 141716A. a pyrazole derivative, was reported by the Sanofi group to be a highly potent. orally active and selective antagonist for CB_1 receptors. However, they did not describe the synthesis of SR 141716A and demonstrate its *in vivo* antagonism lo the cannabinoid agonist Δ^{9}-THC. We now describe a facile synthesis of SR141716A from 4'-chloropropiophenone in a four step sequence in an overall yield of 12%. In pharmacological experiments we sought to demonstrate whether *in vivo* antagonism of Δ^{9}-THC by SR141716A could be demonstrated in two behaviors typically evaluated in the mouse cannabinoid model, and to also determine if the antagonist was efficaious when administered intravenously. It was found that pretreatment of mice with 1 mg/kg (i.v.) of SR 141716A before administration of 1mg/kg (i.v.) of Δ^{9}-THC, antagonized the temperature lowering response (100%) and the locomotor activity (68%) due to Δ^{9}-THC, in a statistically significant manner. These results are consistent with the report that SR141716A is a cannabinoid antagonist. In addition several analogs of SR141716A were synthesized in which the amide bond of SR141716A was replaced by an oxomethylene group and their binding affinities (Ki's) were determined.

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EVALUATION OF CANNABINOID BINDING IN A CB2 CELL LINE

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Although a peripheral receptor for cannabinoid drugs (CB2) exists, it has not been subjected to the same extensive investigation as the brain cannabinoid receptor (CB1). The purpose of this structure-activity relationship study was to examine the binding requirements of the CB2 site. CB2 cDNA was subcloned into the pcDNA3 mammalian expression vector. The CB2 construct was transfected into CHO cells using a calcium phosphate procedure. Stable transformants were selected by adding G418 to the culture media. Colonies of transformed cells were tested for CB2 expression by Northern blot analysis. Cell lines that showed moderate to high levels of receptor RNA were tested in a filtration based radioligand binding assay. Scatchard-Rosenthal analysis of [^{3}H]CP-55,940 binding to P2 membranes prepared from one of the CB2 cell lines (CB2-3) indicated a B_{max} of 3.5 ± .70 pmol/mg protein and an apparent K_d of .686 ± .10 nM. The ability of several compounds to displace [^{3}H]CP-55,940 was determined. These compounds included classical and nonclassical cannabinoids, aminoalkylindoles, anandamide, anandamide analogs and the cannabinoid antagonist SR141716A. The K_i values were compared with K_i values determined using P2 membranes prepared from a CB1 cell line and with K_i values determined using P2 membranes prepared from rat brains. Cannabinol and WIN-55,212-2 were found to have CB1/CB2 K_i ratios of 12.8 and 9.9, respectively. SR141716A and halogenated anandamide analogs were found to have low CB1/CB2 ratios.

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APPROACHES TO RADIOLABELING THE CANNABINOID ANTAGONIST SR141716A AND DERIVATIVES

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Last year Sanofi researchers reported the development of a novel pyrazole cannabinoid antagonist, SR141716A. As part of our ongoing study of the cannabinoid receptor, we are engaged in the preparation of radiolabeled variants of SR141716A. Initially, we have prepared an unsaturated analog that should be amenable to the preparation of tritiated SR 141716A. The synthesis of the unsaturated analog begins with deprotonation of 4'-chloropropiophenone (LDA/THF) and quenching with diethyl oxalate to give ethyl[4-(4-chlorophenyl)-3-methyl-2,4-dioxolbutanoate (**1.**) Refluxing **1** in ethanol with an equimolar amount of 2,4-dichlorophenylhydine hydrochloride furnished the pyrazole ester: 5-(4-chloropheay1)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid ethyl ester. Hydrolysis (NaOH/MeOH), formation of the acid chloride (thionyl chloride, reflux), and formation of the acyl hydrazide (N-amino-1,2,3,6-tetrahydropyridine, Et_3N, CH_2Cl_2, DMAP) gave the unsaturated analog: N-(1,2,3,6-tetrahydropyridin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dich1orophenyl)-4-methyl-1H-pyrazole-3-carboxamide (**2.**) Selective hydrogenation of **2** was accomplished with 5% Rh on carbon (1 atm H_2, EtOH) to give SR141716A which was identical with a sample prepared by an alternative route. Substitution of tritium for hydrogen in the final reduction step should allow for the preparation of tritiated SR141716A.

CHANGE IN QUANTITATIVE EEG "ALPHA HYPERFRONTALITY" DURING AND FOLLOWING INHALATION OF THC

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Using a counterbalanced dose presentation and controlled smoking procedure, eight normal causal THC users smoked placebo (0.0%). low dose (1.77%) and high dose (3.54%) THC cigarettes a week apart. Analong 21 channel EEG was recorded before, during, and immediately after smoking and at 26 minutes, one hour, and four hours post smoking. Blind (to dose) EEG quantification was done at baseline, first and second half of smoking, and all post smoking periods. During smoking, EEG epochs were selected during the periods after exhalation and before the next inhalation. A composite measure of "alpha hyperfrontality" was calculated at each of the time points described above for all Ss. For each dosage condition (placebo, low, high), alpha hyperfrontality scores (and subscores for frontal alpha absolute and relative power and coherence) were subjected to a one way repeated measures ANOVA across baseline, smoking and post smoking periods. Significant EEG change did not occur under placebo or low dose smoking. High dose significanlty increased alpha hyperfrontality with peak elevations for individual subjects ranging from the first half of smoking to the immediate post smoking period. High dose THC also significantly decreased alpha frequency at both anterior and posterior electrode locations.

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EFFECTS OF SMOKED MARIJUANA OF VARYING POTENCY ON PUPILLARY SIZE AND RESPONSE TO DIM AND BRIGHT LIGHT

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Previous studies of the effects of marijuana (M) on pupil size have yielded conflicting results, including an increase, decrease or no change in pupil diameter (diam), possibly due to differences in sensitivity of the measurement methods, conditions of illumination or doses of THC used. In two placebo-controlled, double-blind crossover studies, we used a highly sensitive infrared/video-based system to determine the pupillary responses of non-naive M users to M of varying potency. Pupils were stimulated by an LED of varying intensity: off, dim (8 ft-candles) or bright (20 ft-candles). Under dim and bright conditions, 3 parameters of pupil diam were determined: minimum ($diam_{min}$); final just before cessation of illumination; and mean. In Study I, on three separate days, 11 habitual M smokers (age 40±18 yrs) without ocular pathology underwent pupil size measurements before and at 15, 45, 90 and 135 min after smoking 832, 840 or 751 mg M with 0% (placebo), 1.8% (15 mg) or 3.6% (27 mg) Δ^9-THC. In Study II, a similar protocol was used with only 0 and 3.5% M. Repeated measures ANOVA was performed for minimum, final and mean diameter. Results Study I: Pupil $diam_{min}$ was approximately 22% and 13% larger within 15 minutes after 3.5% M than placebo in both dim and bright light, respectively ($p<.01$); the dilator effect of M was sustained for up to 90 minutes with bright light. Results from Study II replicated the effects of THC on $diam_{min}$ in bright, but not dim, light. No significant effects of M on final or mean pupil diam were noted in either study. Conclusion: M (3.5% THC) consistently increased pupil $diam_{min}$ in bright light but had no discernible or consistent effect on pupil size under dark or dim light conditions or on average pupil size under any conditions of illumination, suggesting a weak pupillary dilator tendency that is discernible only in the maximally light-constricted pupil.

QUANTTTATTON OF TETRAHYDROCANNABINOL AND METABOLITES IN HUMAN HAIR BY GC/MS

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A sensitive and specific method for the quantitative determination of tetrahydrocannabinol (THC) and its major metabolites in human hair has been developed. This was accomplished by modifying our pre-existing analytical method for the analysis of cannabinoids in plasma. Deuterated internal standards of THC, COOH-THC and OH-THC were added to 20-mg hair samples and digested overnight at 37°C in 1N NaOH. Fourteen calibration standards containing known concentrations of THC and metabolites dried onto human hair were also prepared and digested. Digest solutions were extracted with a modified liquid-liquid extraction procedure. Extract residues were derivatized and analyzed on a Finnigan 4500^{TM} mass spectrometer in negative-ion chemical ionization mode with methane reagent gas, helium carrier gas and a Restek 200^{TM}- 30M-0.25µ capillary column. The assay was linear to 50 ng/mg ($r<0.98$) for all three analytes and is capable of detecting 5 pg of THC and COOH-THC on column. Inter-assay precision (n=6 each analyte) was determined to be 7% (THC), 14% (OH-THC) and 8% (COOH-THC). Recovery studies were also performed at 25 pg/mg, 1 ng/mg and 10 ng/mg for each analyte. The method is currently being used to quantitate THC and its metabolites in human hair obtained from known marijuana users. THC has been detected in human hair, but OH-THC and COOH-THC are below the limit of quantitation for the assay.

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SENSITIZATION OF PREFRONTAL CORTICAL NEURON ACTIVITY DURING WITHDRAWAL FOLLOWING CHRONIC COCAINE

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Acute cocaine treatment induces immediate early gene (IEG) expression in rat striatal neurons, which is attenuated by repeated cocaine treatment. In contrast, behavioral sensitization is induced by repeated treatment. Therefore, we examined the expression of *zif*268, an IEG that is highly responsive to neural stimulation, following cocaine challenge (30 mg/kg, i.p.) after two weeks of repeated daily cocaine (10 mg/kg, i.p.) or saline vehicle treatment, or three or seven days withdrawal. We hypothesized that *zif*268 mRNA would be induced to a greater extent by cocaine challenge during withdrawal than following acute or chronic exposure in selected brain regions. Brain sections obtained from male Sprague-Dawley rats one hour after challenge were hybridized with ^{35}S-labeled oligodeoxynucleotide probe complementary to the sequence encoding amino acids 2-16 of the *zif*268 protein, and exposed to liquid photographic emulsion. Quantitative assessment of neuronal labeling determined that acute cocaine significantly increased *zif*268 mRNA expression in neurons of the medial prefrontal cortex (PFC), nucleus accumbens shell, olfactory tubercle (OT) and caudatoputamen, while chronic cocaine attenuated *zif*268 induction in all these regions. *Zif*268 response to cocaine challenge gradually increased during withdrawal to a level that was significantly greater than that produced by acute cocaine challenge only in the infralimbic PFC and OT. Such a differential enhancement of neuronal response to cocaine challenge implicates PFC neuronal circuits in behavioral sensitization, which might be an important component of relapse during cocaine withdrawal.

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7-NITROINDAZOLE ATTENUATES THE INDUCTION AND EXPRESSION OF SENSITIZATION TO COCAINE

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We have previously demonstrated that the nitric oxide synthase (NOS) inhibitors N^G-nitro-L-arginine methyl ester and NG-nitro-Larginine prevent the development of sensitization to the convulsive effect of cocaine (*cocaine kindling*). Unlike the NOS inhibitors we used, 7-nitroindazole (7-NI) is considered as a relatively selective inhibitor of the *neuronal* NOS isoform. The present study was undertaken to assess the effect of 7-NI on the induction and expression of cocaine kindling. A rating scale for the behavioral effects produced after repeated administration of 35 mg/kg cocaine (i.p.) to Swiss Webster mice pretreated with either vehicle or 7-NI (25 mg/kg; i.p.) for ten days was generated. A time-dependent increase in stereotypy and stage four and live seizures was observed in the vehicle/cocaine but not in the 7-NI/cocaine group. A challenge cocaine injection (35 mg/kg) given to all animals following one or ten days drug free period indicated that the pretreatment with 7-NI prevented completely the development of stage four and live seizures, and also attenuated cocaine-induced stereotypy. In addition, a single injection of 7-NI (25 mg/kg) given to cocaine sensitized animals, 15 minutes before cocaine, blocked the expression of cocaine-kindled-seizures and attenuated the expression of cocaine-induced stereotypy. The present study suggests that blockade of brain NOS prevents the *induction* and expression of cocaine kindling.

NEUROTRANSMITTER TURNOVER DURING COCAINE SELF-ADMINISTRATION

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This study used a triad-littermate design lo evaluate the importance of response dependency to the effects of ongoing cocaine administration upon brain biogenic monamine and amino acid neurotransmitter turnover rates. Each member of a triad was exposed to one of three conditions. Cocaine infusions (0.33 mg/inf) were used to engender and maintain lever pressing by one rat under an FR 2 schedule, while the second and third rats received simultaneous infusions of either cocaine or saline, respectively. After a mean of 30 days of exposure to the three treatment conditions and one hour after the session was started the triads were pulse labeled with ^{14}C-glucose, ^{3}H-tyrosine, and ^{3}H-tryptophan. Turnover rates in cortical brain regions were calculated and compared across treatment conditions. Perhaps the most intriguing changes were those seen in the yoked-cocaine group that were reversed in the rats that were self-administering the drug. These included reversals of changes in the prefrontal cortex, motor cortex, and somatosensory cortex. Moreover, the self-administration of cocaine resulted in a great decrease in GAB A turnover in the olfactory cortex. These data indicate that the self-administration of cocaine can diminsh some of the changes induced by the pharmacologic actions of the drug.

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THE AUGMENTED DOPAMINE TRANSMISSION IN ACCUMBENS SHELL AFTER DAILY COCAINE IS CALCIUM-DEPENDENT

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Twenty one days following seven daily ip cocaine injections, we monitored dopamine in the nucleus accumbens core and shell during the application of amphetamine (0.03, 0.3, 3.0 and 30.0 mM) through the probe. These data revealed that the local administration of amphetamine produced a significant increase in accumbal dopamine in saline pretreated animals. Among cocaine pretreated rats, there was a significant potentiation of accurnbal dopamine release only following amphetamine administration into the shell. In order to determine if this sensitized dopamine release was calcium-dependent, we repeated the above shell experiment in the presence and absence of the L-type calcium antagonists, verapamil and diltiazem (100 and 10 μM, respectively, co-perfused with amphetamine) as well as the N-type calcium channel antagonist, conotoxin (1μM) In the presence of these calcium channel antagonists, the sensitized dopamine transmission in the shell was no longer present, although amphetamine-induced release in control rats was unaffected. Taken together, these results indicate that 1) the augmentation in nucleus accumbens dopamine transmission that is associated with cocaine-induced behavioral sensitization occurs primarily in the shell and not the core and 2) that calcium plays an important role in this sensitized dopamine transmission.

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DEVELOPMENTAL DIFFERENCES IN DOPAMINE NEURO-TRANSMISSION AND UPTAKE INHIBITION IN THE RAT CAUDATE

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To understand the long-term effects of cocaine **on** the developing brain, it is first necessary to understand the ontogeny of the systems on which it acts. In the adult brain, cocaine elevates extracellular dopamine (DA) by inhibiting its reuptake. The low density of DA terminals and uptake sites in the developing brain predict that cocaine would raise extracellular DA less effectively in young animals. In the present study, the electrochemical detection method of fast-cyclic voltammetry was used in slices to characterize normal DA release and uptake in the developing caudale after electrical stimulation, and assess the effects of competitive uptake inhibition by cocaine. The concentration of DA released per pulse was higher in adults, 3.8 μM, and 0.64 μM in 12 day old rats. While the Km for uptake was assumed to be the same for both ages (0.2μM), the temporal pattern of DA disappearance was protracted in pups, with a half-time (t1/2) for clearance about 100% greater than adults. Cocaine significantly raised the transporter K_{mapp} in pups, but less effectively than adults. This was shown by a K_i for uptake inhibition by cocaine of 0.3 μM in adults and 1.8 μM in pups. Despite this, the t1/2 of DA disappearance with cocaine was similar between the two ages. These results suggest that developing neurons can mount a substantial response to cocaine, despite their relative immaturity.

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THE ROLE OF GABAA RECEPTORS IN ALCOHOL TOLERANCE AND ALCOHOL-DIAZEPAM CROSS TOLERANCE

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Chronic exposure to alcohol or benzodiazepines results in tolerance and dependence. Furthermore, selective benzodiazepines confer cross tolerance to alcohol. The molecular basis of this tolerance and cross tolerance is unknown, but the GABAA/receptor complex has been suggested as an important site of action (1). Experimental evidence for this comes from studies of Ro 15-4513, the so-called alcohol antagonist, and its reported ability to reverse some of the acute intoxicating actions of alcohol in rodents. If the $GABA_A$ receptor complex mediates some of the acute inhibitory actions of alcohol, then it should also be an important focus for changes resulting from chronic alcohol administration. This study sought to determine the role of the GABAA/receptor in mediating tolerance lo alcohol, and diazepam-alcohol cross tolerance. To facilitate this, Ro 15-4513 and the benzodiazepine antagonist flumazenil were used to block the $GABA_A$ receptor during chronic tolerance and cross tolerance studies respectively. During the chronic study, alcohol and Ro 15-4513, or diazepam and flumazenil were administered for four days. Alcohol induced ataxia and hypothermia were used as a measure of tolerance and cross tolerance on day six. Flumazenil attenuated the development of cross tolerance to both the hypothermic and ataxic effects of alcohol ($P < 0.01$, Dunnett Multiple Comparisons test). In contrast, Ro 15-4513 attenuated the development of tolerance to the ataxic effects of alcohol ($P < 0.01$), but had little effect on the development of tolerance to the hypothermic effects.

In conclusion, the $GABA_A$/receptor complex appears to mediate tolerance and cross tolerance to the ataxic actions of alcohol. Howevcr, the failure of Ro 15-4513 to attenuate tolerance to the hypothermic effects of ethanol suggests that temperature is not completely mediated via the $GABA_A$ receptor complex. Alternatively, this result may simply reflect the partial inverse agonist properties of Ro 15-14513. Further studies with other partial inverse agonists *e.g.* , FG 7142 may help to resolve this issue.

EFFECTS OF INVERSE AGONISTS AT $GABA_A$ RECEPTORS ON ACQUISTION AND PERFORMANCE OF CONDITIONAL DISCRIMINATIONS IN MONKEYS

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High efficacy positive allosteric modulators (triazolam and alprazolam) of GABA action at $GABA_A$ receptors have been shown to disrupt learning and memory in monkeys. In contrast, the partial allosteric modulators of this same receptor will block the action of high efficacy positive allosteric modulators while having little or no effect no learning when administered alone. While the effects of high efficacy and partial allosteric modulators of $GABA_A$ receptors are known, relatively little is known about the actions of the inverse agonists of GABA action at $GABA_A$ receptors in monkeys. The present series of studies was designed to characterize the effects of the full inverse agonist ß-CCE, the partial inverse agonist FG7142, the benzodiazepine receptor antagonist flumazenil and the hallucinogenic ß-carboline derivative harmine on the repeated acquisition and performance of conditional discriminations. When administered alone, these compounds dose-dependently decreased the overall rate of responding with little or no effect on percent errors in both the acquisition and performance components. Flumazenil had little or no effect on percent effors in both components but dose-dependently attenuated the rate-decreasing effects of ß-CCE. Taken together, these results suggest that unlike the high efficacy positive allosteric modulators, the inverse agonists do not disrupt learning and memory under these conditions.

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THE SOCIAL CORRELATES OF HIV INFECTION AMONG WOMEN ARRESTEES IN NEW YORK CITY

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National Development and Research Institutes, Inc.

Knowing the social correlates of HIV infection within the arrestee population will enhance the ability of criminal justice authorities to detect and refer HIV-positive women arrestees to appropriate AIDS-related services. Nearly one-fourth of all women arrested in Manhattan are HIV-positive. This analysis uses logistic regression to profile the social correlates of HIV status among a sample of women arrestees. The data derive from the Drug Use Forecasting Survey, which conducts quarterly interviews of arrestees during booking and collects urine specimens for drug testing. Additionally, the sample of 323 women were screened for HIV using a Calypte urine test. Positive screens were confirmed by Western Blot tests. Contrary to expectations, many of the factors usually associated with the increased likelihood of being HIV-positive (*e.g.,* multiple partners, injection history, race) were not statistically significant. When injectors were examined separately, having children, lacking a high school education, having more than ten sex partners in the last year, and being on public assistance increased the likelihood of being HIV-positive. Among non-injectors, no explanatory factors were significant. These findings underscore the need to develop mechanisms to identify women arrestees who are HIV-positive and to refer them to services that address the needs of HIV-positive women and their children and to develop strategies to enhance the cooperation between criminal justice agencies, health care providers, and social welfare professionals.

AIDS RISK REDUCTION AMONG RUNAWAY AND HOMELESS ADOLESCENTS

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To assess the effectiveness of a peer-led intervention model in reducing drug and sex risk factors for AIDS, 244 youths aged 19 years or less were recruited for paid interviews from a drop-in facility for runaways. Approximately one-half of the youths received eight hours of a "peer helper" intervention designed to train them to serve as AIDS prevention advocates and educators for their peers; the remaining half were assigned to a non-intervention comparison group. Youths were interviewed at baseline, 24 hours later, and at three months. Time-two interviews were obtained on 88% of the initial cohort, while 60% were interviewed at time-three. Measures included conduct disorder (CD), AIDS knowledge, background, drug, and sex behaviors. Youth were at extreme risk for AIDS: 39% had used cocaine, 7% heroin, 12% other opiates, 25% crack, and 6% had injected drugs; 99% reported previous sexual intercourse, including 88% in the preceding three months (mean partners = 2.6), 24% had exhanged sex 19% reported sex with an IDU, and use of condoms was infrequent. In addition, 55% had a diagnosis of Conduct Disorder. Follow-up at three months showed significant knowledge gain by intervention participants compared to controls, however, behavior was not effected by the intervention. Youth with a diagnosis of CD and youth with greater AIDS knowledge reported higher risk behaviors than youth without CD and youth with less knowledge.

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RISK BEHAVIOR FOR AIDS IN OPIOID DEPENDENT PATIENTS SEEKING TREATMENT: A FRENCH SURVEY

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The **objective** of this study was to evaluate AIDS related risk behavior and depression among **subjects** with opioid dependence (DSM III-R) seeking treatment. All subjects were assessed to determine their pattern of illicit drug use, depression, needle use and sexual behavior. The instruments used were the Addiction Severity Index (ASI); the Risk for AIDS Behavior Questionnaire (RAB), a self administered questionnaire that assesses both needle-sharing and unprotected sexual activity; and the Beck Depression Inventory (BDI). **Results** are presented on the initial 57 subjects of which 42 were males (74%). Mean age was 31 years. Mean ASI severity scores for Drugs was 6.44. Thirty-seven subjects (65%) reported having shared needles and other related paraphernalia over the prior six months. Preliminary analysis revealed that ASI Severity ratings, heroin use and BDI scores worsened as sharing activity increased. Thirty percent of the sexually active subjects reported using condoms all the time. There was no correlation found between sexual activity and depression. **Conclusion:** This is the first French study reporting on the quantitative assessment of AIDS risk behavior among opioid dependent subjects. This is an important area of study because the HIV conversion rate is 35-40% among IVDU in France. There is an on-going major informational campaign in France to educate IVDU's about the various risk behaviors for AIDS. Despite this campaign, most subjects seeking treatment continue to share needles.

PSYCHOPATHOLOGY AND HIV RELATED RISK BEHAVIORS IN A SAMPLE OF INTRAVENOUS DRUG-USERS ADMITTED FOR DETOXIFICATION

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The present study was conducted to determine the relationship between the existence of psychopathology and the maintenance of HIV related risk behaviors in a sample of injection drug users. Forty-eight opiate-dependent patients admitted to the Detoxification Unit of the Hospital Clínico Universitario of Valencia (Spain) were divided into two groups according **on** whether or not they had engaged in needle sharing in the previous six months; 17 patients (35.4%) shared needles and 31 (64.6%) did not. The groups were compared using the following: clinical history, HIV-related risk behaviors questionnaire, Beck Depression Inventory (BDI), Symptom Checklist-90 (SCL-90), and the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II). Statistical analysis was performed using the X^2 test for categorical data; Fisher's exact test was employed when sample size was insufficient to calculate $\hat{X}^2$. Two-tailed Student's t test was used for comparison of means with interval data. Patients who shared needles in the previous six months had significantly more diagnoses of antisocial personality disorder ($p<.001$) and of borderline personality disorder ($p<0.005$), than those not engaging in such risk practices. Moreover, patients who shared needles scored significantly higher in the Somatization ($p<.002$), Depression (<.01), Anxiety (<.001), Hostility (<.002), Paranoid Ideation (<.02) and Psychoticism (<.001) scales, and the General Symptom Index (<.001) of the SCL-90, as well as significantly higher scores on the BDI (<.05). In addition, patients who shared needles had significantly more diagnoses of current henzodiazepine dependence (<.05). The present results suggest that psychopathology is significantly associated with higher levels of HIV risk taking behaviors among opiate dependent patients.

PSYCHIATRIC DISORDERS OF OPIOID ADDICTS ENTERING TREATMENT AND RELATIONSHIPS TO AIDS RISK BEHAVIOR

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Risk for AIDS behavior and its relationship to psychopathology was examined as part of a randomized clinical trial evaluating the efficacy of behavioral treatment procedures with opioid addicts. Subjects were assessed at intake using the Addiction Severity Index (ASI), Beck Depression Inventory (BDI), SCL-90-R. Social Adjustment Scale-Self Report (SAS-SR), and Risk Assessment Battery (RAB). At least one month after intake, Ss were evaluated for psychiatric disorders using the Structured Clinical Interview for the DSM-III-R (SCID-P and SCID-II editions). The most frequent Axis I lifetime diagnosis (excluding dependency diagnoses) was Affective Disorder (24.5%), followed by Anxiety Disorder (16.5%). The most frequent Axis II diagnosis was ASPD (31.3%). Of the 234 &entered into the trial, 200 Ss completed both the RAB and SCID interviews. The majority of Ss were male (73.1%) and Hispanic (81.6%). Average age was 37 years. Previous research has found associations between needle sharing and ASPD and depression in opioid addicts. In the present study, a relationship between psychopathology and RAB score was hypothesized. The RAB is a comprehensive self-report measure of AIDS risk behavior, including needle sharing, which provides drug, sexual, and overall risk scores. Contrary to prediction, no relationship was found between the RAB and psychiatric diagnosis. However, using Bonferroni adjustments ($p<.10$), total RAB score was found to be significantly correlated with scores on the BDI ($r=.19$), SCL-90-R Depression subscale ($r=.19$) and PST ($r=.20$), and SAS-SR ($r=.24$). This suggests that self-rated clinical symptoms may be useful as predictors of AIDS risk behavior. Additionally, high risk behavior was related to more severe drug ($r=.28$) and legal ($r=.29$) problems on the ASI.

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HIV RISK BEHAVIOR PROFILES OF METHADONE MAINTENANCE CLIENTS BY GENDER, SEXUAL ORIENTATION, AND SEX-WORKER STATUS

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The goal of this present study was to compare HIV-risk profiles of addicts enrolled in the Los Angeles Enhanced Methadone Maintenance project, a research demonstration project funded by NIDA. Data are from interviews conducted with 500 subjects upon enrollment in the treatment program. Differences in background characteristics and HIV-risk behaviors were analyzed by gender, sexual orientation, and sex-worker status. Women were at greater risk for psychiatric hospitalization, suicide attempts, and psychiatric medication than men. Men were at greater risk than women for sharing their needle-works with strangers, unsafe needle use, and using a condom less than half the time. Gay/bisexual women were at higher risk for on background variables and mental health indicators than heterosexual women. Gay/bisexual males were at greater risk for polydrug use and mental health indicators than heterosexual men. Gay/bisexual male sex-workers were at greater risk than gay/bisexual male non-sex-workers for engaging in cocaine use, unsafe needle use, sharing needle-works with a drug buddy, sharing works with a sexual partner, having unsafe sex, and having vaginal sex without a condom. Heterosexual female sex-workers were at greater risk than heterosexual female non-sex-workers for unsafe needle use, sharing works with a drug buddy or sex partner, having unsafe sex, and engaging in receptive anal sex without a condom. It seems from these analyses that what might have once been characterized as gender differences are more complex. Those individuals at the most direct risk for contracting HIV, though, are sex-workers, particularly gay/bisexual men and heterosexual women. They are engaging in polysubstance abuse, unsafe needle use, unsafe sex, and more illicit activities.

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DIFFERENCES BETWEEN HIV-POSITIVE AND HIV-NEGATIVE COCAINE USERS ON A SELF-REPORT NEUROPSYCHOLOGICAL IMPAIRMENT SCREEN

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The Neuropsychological Impairment Scale (NIS: O'Donnell, *et. al.,* 1994) was administered to 40 methadone-maintained patients upon entry into treatment for cocaine dependence and again at treatment completion. Pre-treatment, HIV-positive cocaine users (N = 18) reported significantly more impairment than did HIV-negative patients (N = 22), and scored in the impaired range relative to normative data. HIV-positive patients reported less impairment post-treatment; however, this reduction was significant only if abstinence from cocaine was initiated. The HIV-positive patients who continued to use cocaine remained in the impaired range. The HIV-negative patients who did not initiate abstinence from cocaine reported increased impairment post-treatment.

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MANAGEMENT OF HIV MEDICATIONS IN METHADONE TREATMENT

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A random assignment pilot study with methadone maintenance patients who have HIV disease indicates the feasibility of providing medication management for AIDS medications. Medication management is a promising intervention that has been used widely with the elderly but has not been well tested with substance abusers. This pilot aimed to (1) derermine the feasibility of delivering a medication management program and (2) estimate the effect size of adding medication management to simple on-site dispensing of AIDS medications. Outcomes focused on adherence to AIDS medications measured by self report, pill count, and opening the medication bottle as scheduled. Twelve methadone maintenance patients with symptomatic HIV disease were recruited and randomly assigned to an eight week intervention involving on-site dispensing of AIDS medications with or without medication management (delivered by a paraprofessional counselor in a protocol developed for the study). Of the patients, 50% were women; 17% were African-American, 17% Hispanic, 50% caucasian, and 16% other. The patients were prescribed a mean of 6 medications in addition to methadone. Primary AIDS medications included Septra (83% of patients), AZT (50%), Mycelex Troches (25%), and fluconazole (25%). All 12 patients completed the protocol, 8-week followups, and 12-week followups. Eight participated in a post-followup focus group. Five of six were engaged by the medication manager, measured by contact and follow-up interviews. Followup data indicated no significant differences between groups and few indicators that medication management added significantly to the effects of on-site dispensing. Self-reports of medicalion adherence at all followup points were significantly ($p < .01$) improved over baseline. Process evaluation indicated that the major medication management activities were tracking adherence, providing general encouragement, and dealing with mood or mental status of patients. Feedback from the focus group indicated that medication management helped patients to fill prescriptions, establish a routine for taking medications, institute reminders, and strengthen motivation for adherence during the start-up time when patients were experiencing new medications and side-effects. We conclude that medication management is feasible and merits further investigation to improve patients' adherence to AIDS medications.

EFFECTS OF PHENCYCLIDINE, PENTOBARBITAL AND DIAZEPAM IN COMBINATION WITH FLUMAZENIL ON WORKING MEMORY

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A titrating matching-to-sample schedule of reinforcement was used as a model of working memory. During the first five trials of each session, the delay was fixed at three seconds in length. On the sixth and all subsequent trials the length of the delay either increased, did not change, or decreased such that accuracy was maintained al approximately 80%. In the squirrel monkey phencyclidine (0.03 - 1.0 mg/kg), pentobarbital (0.1 - 10 mg/kg) and diazepam (0.3 - 10.0) produced dose dependent decreases in both mean delay and response rate. Flumazenil (0.1 - 10 mg/kg) alone had no effect on mean delay or response rate. When selected doses of flumazenil were administered in combination with these drugs, the rate decreasing effects of diazepam and phencyclidine, but not pentobarbital, were reversed. Flumazenil did not antagonize any of their effects on mean delay. In the pigeon phencyclidine (0.03 - 3 mg/kg), pentobarbital (0.3 - 10 mg/kg) and flumazenil (0.003 - 1.0 mg/kg) decreased both the response rate and mean delay. Diazepam (0.03 - 3 mg/kg) only decreased the mean delay value. Selected doses of flumazenil in combination with these drugs failed to antagonize the effects of each of these drugs in the pigeon. This suggests a species difference and a possible difference between drug effects on rate of responding and working memory.

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GENERALIZATIONS BETWEEN MIXTURES OF DRUGS UNDER "AND"- AND "AND-OR" DISCRIMINATION PROCEDURES IN RATS

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In order to explore the characteristics of discriminations based on drug mixtures, tests of generalization from mixtures of one pair of drugs to another were carried out. Two-lever operant procedures with food reinforcement were used throughout. Two groups of rats (11=8-10) were trained to discriminate a mixture of amphetamine plus pentobarbitone from saline or a mixture of nicotine plus midazolam from saline (AND procedure). Two additional groups of rats (n=8-9) were trained to discriminate the same mixtures from either of their constituent drugs alone (AND-OR procedure). Dose-response tests of generalizations from either mixture to the other one and to its component drugs were then carried out. In the AND procedure, cross-generalization between the two mixtures was nearly complete (maximum responses of 74-90%); there was also partial generalization (43-64%) from either mixture to the component drugs of the other. In the AND-OR procedure, cross-generalization between the mixture was never more Than partial at any dose tested (38-51%); there was either no or partial generalization (11-37%) from either mixture to the component drugs of the other. Thus, the experiments demonstrated that one mixture of drugs can generalize to another mixture and that the type of training procedure can very markedly influence the extent of this generalization. Furthermore. partial generalizations to the component drugs were greater under the AND than under the AND-OR procedure; taken as a whole, The results suggest that training under the AND-OR procedure may confer increased pharmacological specificity.

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EFFECTS OF REGULAR MARIJUANA SMOKING WITH OR WITHOUT TOBACCO ON CHANGE IN LUNG FUNCTION: A LONGITUDINAL STUDY

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Cross-sectional studies have revealed conflicting effects of habitual marijuana (M) smoking on lung function; some studies have shown no impact on lung function while others have shown obstructive ventilatory defects additive to those associated with tobacco (T) use. To further evaluate the pulmonary effects of regular M use, we conducted a longitudinal study of lung function in a convenience sample of 394 healthy males (age 33±6 yr) and females (age 34±7 year), including, at entry, 131 (77% male) habitual smokers (S) of M alone (MS), 112 S (72% male) of M+T (MTS), 65 regular S (51% male) of T alone (TS) and 86 nonsmokers (62% male) of either substance (NS). Forced expired volume in 1 sec (FEV_1) was measured at study entry and in 255 subjects on 1-6 additional occasions at intervals >1 year. Random effects models were used to estimate mean rates of decline in FEV_1 with age in relation to M or T smoking status at any point in time and lo compare these rates between smoking groups classified as never, intermittent or continuing S of M or T. Results: Males showed a significant effect of T, but not M, on FEV_1 decline ($p<0.05$); no additive or interactive effects of M+T were noted. Among females, decline in FEV_1 due to T smoking was less than in males; M smoking was not associated with greater declines in FEV_1 than nonsmoking. Among males, *intemittent* S of T had greater declines in FEV_1 than never S, while community S had the greatest declines: no significant effect of *continuing* or *intemittent* M smoking was noted. Females also showed a slight negative effect of T, but not of M, in relation to the continuity of smoking. Conclusion: Regular T, but not M, smoking is associated with greater annual rates of decline in lung function than nonsmoking. These findings do not support an association between regular M smoking and obstructive pulmonary disease.

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NICOTINE AND COCAINE DYNAMICS: PRIVATE PATTERNS AND CONSEQUENCES

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This study explores the dynamic links between tobacco and crack cocaine smoking in 113 male addicts. A longitudinal retrospective Natural History methodology, as well as measures of addiction severity, craving, motivations, temptations, confidence and change assessment were used. These subjectsí tobacco addiction averaged in the mid-range of the Fagerstrom Tolerance scale. Most subjects reported that smoking cigarettes significantly increased craving for cocaine. During periods of cocaine use, the subjectsí craving and use of cigarettes increased significantly after using cocaine in comparison to before cocaine use. Subjects stopped using cocaine, either voluntarily or involuntarily, a mean of four times each and quit smoking cigarettes a mean of 1.3 times each. In most cases the reasons for quitting were entering an institution where smoking was prohibited. The majority of the subjects reported crack abstinence facilitated cigarette abstinence. The duration of crack abstinence (>1 month) in those who also quit cigarettes, however, was only half as long as in those smoking. During the initial months of tobacco abstinence, cocaine use dropped dramatically; after three years of tobacco abstinence cocaine use had returned to nearly pre-tobacco-quitting levels. During initial cocaine abstinence, cigarette smoking also dropped substantially. These levels remained relatively stable until much later in cocaine abstinence when cigarette smoking increased to pre-cocaine-abstinence levels. Subjects concurred that, in general, smoking crack cocaine did/would make it more difficult to quit cigarettes. Further time series analyzes are underway.

ORAL COCAINE (OC) AND CARBAMAZEPINE (CBZ) PLUS TRANSDERMAL NICOTINE (TDN) USED FOR COCAINE-SMOKING (COCA PASTE) DEPENDENCE (CCPD) TREATMENT

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Coca paste (CCP) is the most commom and dangerous form of use cocaine in Perú > Colombia > Bolivia > Ecuador > others. CCP is used by smoking, mixed with tobacco in commercial cigarettes (CCPC), and thus is considered as double dependence (cocaine-nicotine). Its rate of relapses with/without treatment is very high (>50%/>75%). CCP contains an average of 49.3% of cocaine alkaloid (CA). In a typical binge CCP-dependents use 20(6-50) CCPC, containing an avg of 3040 mg of CCP (1900 mg of CA), plus 5960 mg of tobacco (80 mg of nicotine). There are reports that OC and CBZ could drop avg of relapses and CCPC use in CCPD. 20 CCP-dependents (DSM-IV), volunt, spanish, mean age 25±7, men, 21.4±14 CCPC/binge, mean 4.224 relapse/ week in the last month, mean 5.2±3 days of largest abstinence in the three last months, enter in a open-label controlled study during three months. Four volunteers used OC (20 mg) + TDN (7 mg) daily; four used CBZ (400 mg) + TDN (7 mg); four used OC (20 mg) alone; four used CBZ (400 mg) alone; four used TDN (7 mg) alone. Results showed that OC + TDN reduce weekly relapse avg (0.3) CBZ + TDN (0.9), OC (1.2), CBZ (2.8), TDN (3.6) and increase largest abstinence' days: 90; 84; 83; 32; 21. Statistical analysis of the results ($p<0.01$) suggest that use of OC+TDN>CBZ+TDN>OC could be an effective treatments in Coca Paste Dependence.

MEDICAL AND PSYCHIATRIC ILLNESSES OF INDIVIDUALS ABUSING A SINGLE DRUG COMPARED TO ILLNESSES OF POLYDRUG ABUSERS

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Medical and psychiatric histories of single drug abusers are seldom compared to the histories of polydrug abusers. Individuals who abuse different. numbers of drugs may possess different medical histories that may or may not reflect medical complications of the substances they abuse. Medical records of 529 single drug and 1,525 polydrug admissions to a hospital inpatient detoxification unit were compared. One hundred and ninety-nine females and 330 males composed the group of single drug abusers, while 564 females and 961 males composed the polydrug abuser group. Numbers and types of substance currently used are collected routinely at admission. Illicit and licit drugs. alcohol, and inhalants are included. Nicotine is not included. Patients were classified as single or polydrug (abuscrs, according to the number of drugs they reported using when admitted. Medical and psychiatric histories of each patient were abstracted. Each medical illness was classified as acute or chronic; current psychiatric illnesses were included. Controlling for age and gender, analysis compared total numbers of acute and chronic medical along with current psychiatric illnesses in single and polydrug abusers. Confidence intervals were constructed; the results indicate a statistically significant increase in chronic illnesses in males beginning at age 31. This increase is not seen in females until age 41. The increase is seen in both single drug and polydrug abusers. A significantly larger number of acute illnesses is seen only in female single drug abusers, ages 31 to 40. No differences were seen in numbers of admissions with current psychiatric disorders within or between genders or drug use groups. As can be expected, individuals younger than age 31 have fewer medical problems in general. Whicn drug users begin to develop chronic illnesses, men develop these a decade earlier than women. Beginning at age 41, female single and polydrug abusers report statistically significantly more chronic than acute illnesses. Male single and polydrug abusers in all age groups report statistically significantly more chronic than acute illnesses. These findings have important implications for drug abuse research and treatment.

CHAOS AND INTOXICATION: DRUG AND ALCOHOL USE IN COMPLEX SYSTEMS

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The pathways to and antecedents of recreational and dependent alcohol and drug use are not clearly understood. For example, the Third Triennial Report to Congress (Department of Health and Public Service, 1991) summarised the wide-range of individual 'risks' which need to be considered. These were categorised as biological (genetic), psychological, behavioural (anti-social and delinquent activities) and demographic (such as gender or ethnic factors), and environmental 'risks' arising from family or peer group influence. But how can sense be made of this complexity? From work in the natural sciences we know that within dynamic systems there are *attractors* (parts of the system which are moved towards) from which motion can a) stay still (steady state), or b) repeat periodically. Steady states and periodic loops arise in settings which are not sensitive to initial conditions. However, there is another form of attractor which is dependent on initial conditions and this has been referred to as a *strange attractor*. With strange attractors the point which represents the state of the system (perhaps in the context of this paper this could be considered to be the extent and context of alcohol or drug use) moves (changes state) in a non-periodic way. The motion on a strange attractor is a time evolution with sensitive dependence on initial conditions (Ruelle, 1991) which is also the definition of chaos (see Ruelle, 1991; Stewart, 1990) for further discussion of the mathematical and physical context of these ideas). But is alcohol and drug use chaotic: that is does it have sensitive dependence on initial conditions?

Recent data on young people in rural settings in the UK (Dean, 1995) point to the existence of a complex system of effects within which forms of intoxication take place. It was argued that drug use outcomes for the individual arose from a specific relationship between aspects of social space, time and individual agency. These elements were; remoteness (distance), proximity (association in social space), incomer influences (new social ideas), individual agency, history (association in time) and material preconditions. In this paper it was contended that small changes in one of these elements can change significantly individual patterns of drug use. In some communities young people used heroin, whereas in others pig tranquillisers were injected. Essentially, therefore, small changes in input conditions led to large outcome effects which could not have been predetermined at the individual level. In this sense it can be argued that alcohol and drug use is thus chaotic and that outcomes for an individual cannot be predicted (in the same way that weather forecast have limited accuracy).

But what does this tell us about clinical practice? If the work of Prochaska and Diclemente is used as an example of a non-chaotic model some insights can be gained (see, for example, Toward a Comprehensive Model of Change. in Miller, W. and Heather, N. Treating Addictive Behaviours, New York: Plenum. 1986). These authors have described a cycle of change through which an alcohol or drug user may pass. They depict five dimensions within this model; precontemplation, contemplation, action, maintenance of new behaviour and relapse. The model describes a periodic motion through these differing stages. However, as has been argued, periodic change of this type only occurs in systems which do not have sensitive dependence on initial conditions. If such sensitivity exists then movement becomes chaotic. That is, a chaos theory of alcohol or drug use would predict that any one individual may or may not enter one of these stages, and that the time spent at any stage would also vary. In essence, even if it were possible to identify without doubt where someone was in the cycle, it could not be known where they would be a the next time interval. This has important implications for treatment and intervention. If the actual clinical condition of a client is unknowable, then chance will play an important part in achieving success with current approaches based on non-chaotic theory. To advance knowledge and test these ideas perhaps we need to look more closely at data which do not support the effectiveness of any specific intervention. That is, perhaps we need to address the "noise" in our data, where findings do not meet basic assumptions.

DOPAMINE TRANSPORTER mRNA MAPPING IN THE RAT BRAIN AND EFFECTS OF "BINGE" COCAINE, WITHDRAWAL, AND DOPAMINE RECEPTOR ANTAGONISTS

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Dopamine transporter (DAT) mRNA was quantified in selected brain regions from individual naive rats by liquid scintillation analysis of trichloracetic acid precipitated RNase-protected mRNA:cRNA hybrids. Densities were determined as the mean (n ≥ 26) ratio of pg DAT mRNA per µg of total RNA: substantia nigra (SN) 7.7±0.47; ventral tegmental area (VTA) 4.1±0.46; central grey 0.39±0.061; amygdala 0.19±0.025; caudate putamen 0.15±0.026; hypothalamus 0.15±0.016; nucleus accumbens 0.13±0.014; pons/medulla 0.12±0.017; globus pallidus 0.13±0.038; pituitary 0.071±0.015; frontal cortex 0.046±0.0062. DAT mRNA levels were measured following various treatment protocols. No changes in DAT mRNA were found in either the SN or VTA following 3 or 14 days of "binge" (3 i.p. injections at one hour intervals starting 30' after lights on) saline or cocaine (15 mg/kg body weight). Similarly, no changes in DAT mRNA levels were observed in the SN or VTA following ten days of withdrawal from 15 days of "binge" saline or cocaine. However, in the VTA. a significant interaction between cocaine and dopamine receptor antagonists ($p<0.005$) was observed following three days of cocaine administered in conjunction with either the D1 dopamine receptor antagonist SCH23390 (COCD1) or the D2 dopamine receptor antagonist sulpiride (COCD2) when compared to the group treated with cocaine alone (COC). Other groups in this study included D1 receptor antagonist alone (SALD1), D2 receptor antagonist alone (SALD2) and saline (SAL). See table (mean±SEM):

SAL (n=9)	COC (n=9)	SALD1 (n=6)	SALD2 (n=6)	COCD1 (n=6)	COCD2 (n=6)
6.05±0.82	4.47±0.56	6.85±0.78	5.21±0.42	8.26±1.21[a]	8.05±1.07[a]

[a] Orthogonal comparisons with the COC group after analysis of variance: F_{COCD1} (1,35)=11.17, F_{COCD2} (1,35)=10.01, Ps<0.005. **ACKNOWLEDGEMENTS:** Supported by NIDA P50-DA05130, DA00049.

CHRONIC D_2-RECEPTOR AGONISTS' EFFECT ON BRAIN DOPAMINE TRANSPORTER IN RATS

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Chronic cocaine exposure induces an increase in binding to the dopamine transporter in post- mortem striatal samples from human cocaine users (Little *et. al.,* Brain Research, 628: 17-25, 1993; Staley *et. al.,* JPET, 271: 1678-1685, 1994). One possible mechanism for the cocaine-ihduced changes in DAT function is through stimulation of the presynaptic dopamine autoreceptor. Experiments have found that the dopamine receptor agonist quinpirole increases striatal synaptosomal dopamine uptake acutely, which is reversed by the addition of sulpiride (Meiergerd *et. al.,* J Neurochemistry, 61: 764-767, 1993). Also, chronic cocaine-induced increases in accumbens' dopamine uptake are blocked by the co-administration of pimozide (D2 antagonist), as measured by *in-vivo* microdialysis (Parsons *et. al.,* J Neurochemistry, 60: 376-379, 1993). These results suggest that stimulation of the dopamine autoreceptor (possibly of the D2 subtype) may increase dopamine transporter (DAT) function through a direct, perhaps even intramembranal, mechanism. The present experiment examined the effect of chronic quinpirole and apomorphine treatments on striatal DAT binding sites. Rats (n=8/group, Sprague-Dailey, males, 250-300 gm b.w.) were injected subcutaneously BID for seven days with either: quinpirole, 0.7 mg/kg b.w.; apomorphine, 2.0 mg/kg b.w.; or saline vehicle. After sacrifice (12 hours after the last injection), brains were frozen at -70°C. Striatal DAT binding was later examined autoradiographically using the DAT-selective cocaine congener, [^{125}I]RTI-121. Binding was assessed at four radioligand concentrations (0.05, 0.5, 1.0 and 5.0 nM). No alterations were detected in DAT binding sites after the present doses of quinpirole and apomorphine. However, another radioligand might have been more sensitive to alterations in DAT conformation.

DOSE-DEPENDENT EFFECTS OF THE D3-PREFERRING AGONIST 7-OH-DPAT.

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Dose-dependent effects of 7-OH-DPAT (DPAT) on several behaviors, including place preference, were assessed. Three two-day conditioning trials were conducted. On one day, animals received one of eight doses of DPAT (0-5 mg/kg, s.c.) and were placed into a distinct compartment for 40 minutes. On the other day, they were injected with saline and immediately placed into a different compartment for 40 minutes. Locomotion, sniffing, and yawning were measured following the first and last injection of DPAT. Place conditioning was assessed the day following the last trial. DPAT produced a U-shaped dose-dependent change in locomotion and sniffing, and an inverted U-shaped dosedependent change in yawning. Additionally, repeated administration of 0.1 mg/kg sensitized yawning, whereas 5 mg/kg sensitized locomotion. None of the doses of DPAT produced conditioned place preference, however, there was a trend for a conditioned place aversion at 0.03 mg/kg. By contrast, LiCl (127 mg/kg) produced conditioned place aversion and amphetamine (1 mg/kg) produced conditioned place preference using identical conditioning parameters. A subsequent experiment demonstrated that the 0.03 mg/kg dose of DPAT produced conditioned place aversion following six conditioning trials. DPAT has a higher aftinity for D3 receptors relative to D2 receptors. Therefore, it is suggested that the intermediate doses (0.01-0.1 mg/kg) that decreased locomotion and sniffing, and increased yawning may preferentially occupy D3 receptors. Furthermore, the results suggest that putative D3-preferring doses of DPAT have weak aversive effects.

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THE EFFECTS OF D-3 RECEPTOR AGONISTS ON COCAINE SELF-ADMINISTRATION ARE MEDIATED POST-SYNAPTICALLY

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Nucleus accumbens microdiaiysate samples were collected during an i.v. self-administration session (FR-5) in which rats were allowed to self-administer cocaine (0.25 mg/inf), a combination of cocaine (0.25 mg/inf) and 7-OH-DPAT (4.0 µg/inf), 7-OH-DPAT alone (4.0 µg/inf), and saline during four consecutive 1.5 hour periods. During cocaine self-administration, DA levels rose to 373±18% of baseline, with an average of 2.3±0.2 cocaine infusions/10 minutes. 7-OH-DPAT reduced the number of drug infusions to 1.1±0.3 infusions/10 minutes, accompanied by a decrease in dialysate DA to a stable level of 134±8% of baseline. Almost immediately after switching the drug solution to 7-OH-DPAT alone, the number of self-administered infusions increased to an average of 9.1±0.3 infusions/10 minutes, while dialysate DA decreased further to a stable level of 37±6% of baseline. The more potent and selective D-3 receptor agonist quinelorane produced similar results at a 16-fold lower dose than 7-OH-DPAT. The addition of quinelorane (0.25 µg/inf) to the self-administered cocaine solution (0.25 mg/inf) reduced cocaine intake by 50% (from 2.4±0.1 to 1.2±0.1 infusions/10 min) while also decreasing dialysate DA from 366±63% of baseline to a stable level of 187±25% of baseline. When quinelorane was self-administered alone (0.25 µg/inf) the number of self-administered infusions increased to an average of 5.3±0.2 infusions/10 minutes, during which time dialysate DA decreased to a stable level of 71±8% of baseline. To test the regional specificity of 7-OH-DPAT, the agonist was locally applied to the nucleus accumbens and ipsilateral striatum of the same animal via reverse dialysis. DA eftlux in the nucleus accumbens was dose-dependently decreased by 7-OH-DPAT while there was no effect of 7-OH-DPAT in the striatum. The effect of 7-OH-DPAT in the nucleus accumbens was dose-dependently blocked by the putative D-3 antagonist nafadotride. Altogether these data implicate postsynaptic D-3 receptors in the nucleus accumbens in the reinforcing actions of cocaine and identify the D-3 receptor as a promising target for new pharmacotherapies for cocaine abuse.

EFFECTS OF 7-OH-DPAT IN RHESUS MONKEYS TRAINED TO DISCRIMINATE COCAINE FROM SALINE

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The effects of the putative dopamine D3 receptor agonist 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT) were examined in cocaine-trained monkeys. Four rhesus monkeys were trained to discriminate cocaine (0.4 mg/kg, i.m.) from saline under a FR30 schedule of food presentation. Under these conditions, doses of cocaine (0.013-1.3 mg/kg) produced a dose-dependent and complete generalization to the training dose of cocaine in all monkeys. The effects of cocaine were antagonized by the non-selective dopamine antagonist flupenthixol (0.018 mg/kg, i.m.) in all four monkeys. The effects of 7-OH-DPAT (0.01-1.8 mg/kg) were inconsistent across monkeys. In two of the four monkeys, 7-OH-DPAT consistently and completely generalized to cocaine and response rates decreased in a dose-dependent manner. Both the cocaine-like discriminative stimulus and rate-decreasing effects of 7-OH-DPAT were antagonized by flupenthixol. The effects of 7-OH-DPAT pretreatment (0.01-0.32 mg/kg) on cocaine's discriminative stimulus effects were examined using a dose-addition model, and 7-OH-DPAT produced either additive or less than 'additive effects. In the other two monkeys, 7-OH-DPAT produced a dose-dependenl decrease in response rates but did not consistently generalize to cocaine. Flupenthixol did not antagonize the rate-decreasing effects of 7-OH-DPAT in these two monkeys. Pretreatment with 7-OH-DPAT (0.1-0.32 mg/kg) either had no effect or produced a rightward shift of the cocaine dose-effect curve. In time-course experiments, 7-OH-DPAT displayed a slower onset and a longer duration of effect than cocaine. In substitution experiments, the D3/D2 dopamine agonist quinpirole completely generalized to cocaine in three monkeys, and partially in the fourth monkey. Quinpirole showed the highest potency in those monkeys in which 7-OH-DPAT consistently generalized to cocaine. The results of this study suggest that compounds showing selectivity for the D3 receptor interact with the discriminative stimulus effects of cocaine. However, the involvement of other dopamine receptor subtypes can not be excluded.

SELECTIVE HIGH AFFINITY DOPAMINE D3 RECEPTOR LIGANDS SUBSTITUTE FOR COCAINE ONLY AT RATE-DECREASING DOSES

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Determining the role of dopamine D3 receptors in mediating the discriminative stimulus effects of cocaine has been limited by the lack of ligands selective for this receptor. Recently, we reported that (±)-7-OH-DPAT (7-hydroxy-2-(di-n-propylamino) tetralin), (0.03-1.0 mg/kg) fully substituted for cocaine in rats trained to discriminate cocaine (10 mg/kg) from saline with an ED_{50} of 0.3 mg/kg (95% CL: 0.27-0.38), but substitution occurred only at doses that severely reduced rates of responding. The D3-selective enantiomer, (+)-7-OH-DPAT, was equal in potency 10 the racemate in substituting for cocaine. In contrast, the (-)-enantiomer (0.1-10 mg/kg) only partially substituted for cocaine. Both enantiomers significantly reduced response rates. The D3 ligand, (+)-PD 128907 (4aR,10bR-(+)-trans-3,4,4a,10b-tetrahydro-4-n-propyl-2H,5H[4,3-b]-1,4-oxazin-9-ol) is approximately 1000-fold more potent at D3 receptors than D2 receptors (deMattos *et. al.,* 1993). a selectivity that exceeds that for any compound studied previously. This compound substituted for cocaine with an ED_{50} of 0.94 mg/kg (95% CL: 0.57-1.54). At doses that substituted for cocaine, there were significant reductions in rates of responding. The reported high degree of selectivity of (+)-PD 128907 for D3 receptors, its substitution for cocaine, and the similar effects of (+)-7-OH-DPAT, suggest that D3 receptor ligands can produce cocaine-like discriminative stimulus effects. but with additional effects on response rate that are not shared with cocaine.

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EFFECTS OF CHRONIC INTRAVENOUS COCAINE ADMINISTRATION ON LOCOMOTOR ACTIVITY AND DOPAMINE D2/D3 RECEPTORS IN RAT BRAIN

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The dopamine D3 receptor has been implicated as a possible mediator of events in reinforcement/abuse of psychostimulants such as cocaine. These studies examined the effect of chronic i.v. cocaine (0.5, 1.0, 3.0 mg/kg) administration for 14 days on D3 receptor density in the striatum and nucleus accumbens and development of behavioral sensitization. Male Sprague-Dawley rats implanted with an intravenous access port (Mactutus, *et. al.,* 1994) were randomly assigned to activity chambers and habituated during two 60 minute test sessions following injection of heparinized saline. Animals were sacrificed 24 hours after the last injection and the density of D3 receptors was determined as previously described using 5 nM [^{3}H](+)7-OH-DPAT (Wallace and Booze, 1995). Chronic cocaine treatment resulted in a significant dose-dependent increase in striatal D3 receptors which correlated with 60 minute central activity over all test days. Conversely, D3 receptors in the nucleus accumbens exhibited significant dose-dependent reductions which were predicted by the initial five minutes of central activity observed on sensitization days (days 6, 8, and 10). Sensitization to the effects of cocaine was dose-dependent with the time to peak sensitization day following the rank order of 0.5 > 1.0 > 3.0 mg/kg. The density of D2 receptors was unchanged in both regions. These data suggest striatal and nucleus accumbens D3 receptor involvement in the both induction and expression of cocaine-induced behavioral sensitization. Thus, the D3 receptors in the striatum and nucleus accumbens may be differentially involved in the locomotor stimulation (striatal D3) and reinforcing aspects (nucleus accumbens D3) of chronic cocaine administration.

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SELF-ADMINISTRATION OF COCAINE AND DOPAMINE D1 AGONISTS UNDER A PROGRESSIVE-RATIO SCHEDULE IN RHESUS MONKEYS

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The selective dopamine D1 receptor agonists, SKF81297, SKF82958 and R(+) 6-Br-APB have been shown to function as positive reinforcers in rhesus monkeys (Weed and Woolverton, 1994, Soc. Neurosci. Abs., 101.6). The present experiment evaluated the relative reinforcing efficacy of these compounds using a progressive-ratio schedule of reinforcement. Rhesus monkeys were prepared with i.v. catheters and lever pressing was maintained by a baseline cocaine (COC) dose of 0.1 mg/kg/inj. Daily sessions consisted of five components, each made up of four trials for a maximum of 20 trials. Within a component each trial had the same fixed-ratio (FR), and the FR increased between components (120, 240, 480, 960, 1920). Time-outs (30 min) separated trials, and trials had limited holds of 15 minutes. Sessions ended after two consecutive incomplete trials. The baseline COC dose alternated with doses of test drugs for a minimum of three days or until responding was stable (+/- one injection/session (inj/sess) of three-session mean). Dose-related increases in both the number of inj/sess and the breakpoint (BP), the maximum completed FR, were seen with COC and the D1 agonists tested. Preliminary data from five monkeys indicated that COC, SKF81297, SKF82958 and R(+) 6-Br-APB all functioned as reinforcers and the maximum BP's of all were 960. However, the maximum number of inj/sess differed among these drugs: COC 16 inj/sess (0.17 and 0.3 mg/kg/inj), R(+)-6-Br-APB 15 inj/sess (0.1 mg/kg/inj), SKF82958 15 inj/sess (0.1 mg/kg/inj), and SKF81297 13 inj/sess (0.3 mg/kg/inj). The maxima for COC and SKF81297 differed significantly, but the other maxima did not. COC, R(+) 6-Br-APB and SKF82958 may function as reinforcers of slightly higher reinforcing efficacy than SKF81297, but all maintain high breakpoints. These findings extend the conditions under which selective D1 agonists can function as reinforcers and are consistent with an abuse-liability for high-efficacy D1 agonists.

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SELF-ADMINISTRATION OF D_1 RECEPTOR AGONISTS: COMPARISON UNDER DIFFERENT SCHEDULES OF REINFORCEMENT

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Dopaminergic mechanisms are believed to play a prominent role in the self-administration of cocaine and other abused stimulants. Although the contribution of D_2 receptors is well established, less is known about the role of D_1 receptors in the reinforcing effects of these drugs. To help clarify the role of D_1 receptors, agonists differing in intrinsic activity at D_1 receptors (SKF 82958, SKF 81297 and SKF 77434) were studied for their capacity to maintain i.v. self-administration in squirrel monkeys previously trained to self-administer cocaine. Each drug was studied under both a fixed-ratio (FR) and a secondorder fixed-interval (FI) schedule of reinforcement. For comparison purposes, the reference D_2 receptor agonists, (+)-PHNO and quinpirole, were also studied under the second-order FI schedule. The high-efficacy D_1 agonist SKF 82958 maintained self-administration under both the FR and second-order FI schedules and had dose-related effects that were qualitatively similar to those of (+)-PHN0 and quinpirole under the latter condition. SKF 81297 maintained self-administration only under the FR schedule and SKF 77434, a low-efficacy D_1 agonist, failed to maintain self-administration under either schedule. The results indicate that high efficacy D_1 agonists can maintain i.v. self-administration in monkeys and are consistent with the view that D_1 receptors may play a pertinent role in the self-administration of cocaine and abused stimulants.

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OPIOID ANALGESIA AFTER SPINAL ADMINISTRATION IN AMPHIBIANS: BINDING AND BEHAVIORAL STUDIES

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Spinal administration of opioid agents produces a well-defined analgesia in mammalian models and in the clinic by acting on specific opioid receptors in spinal tissue. It is not known if similar mechanisms of opioid analgesia or what type of opioid receptors exist in the spinal cord of lower vertebrates. Northern grass frogs, *Rana pipiens,* were assessed for nociceptive thresholds using the acetic acid test and binding assays performed in spinal tissue. Spinal administration of mu (dermorphin, DAMGO, fentanyl, morphine), delta (DSLET, DADLE, DPDPE, deltorphin), and kappa opioids (CI-977, bremazocine, U50488, nalorphine) produced a dose-dependent analgesia. ED50 values for the 12 opioids ranged from 0.04 nmol/frog for dermorphin to 43.1 nmol/frog for nalorphine. Binding experiments using 3H-dipmnotphine demonstrate high levels of opioid binding in frog spinal cord (Bmax=79 pmol/mg). Kappa3 binding (3H-NalBzoH) accounted for 65% of total binding sites. Kappa1 binding (3HU69593) was 10% of binding and only traces of delta (3H-DPDPE) were observed. No mu (3H-DAMGO) or kappa2 (3H-bremazocine) sites were detected However, mu-selective agents were the most potent and kappa-selective agents the least. This *"kappa-like"* binding site showed differences in the binding of mu agents compared to the *kappa3* site described in mammalian CNS. Comments included advice on examining the C-fiber nature of the acetic acid test, an elaboration of the ethical considerations of the amphibian model, and speculation on the lack of correlation on the behavioral and binding results.

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N-CBM-TAMO: A SHORT-TERM OPIOID AGONIST AND A LONG-TERM OPIOID ANTAGONIST

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The antinociceptive and opioid receptor binding properties of the N-cyclobutylmethyl analogue of normorphinone, 14α,14'ß-[dithiobis[(2-oxo-2,1ethanediyl)imino]]bis[7,8dihydro-N-(cyclobutylmethyl)-normorphinone] (N-CBM-TAMO) were investigated. In the mouse 55°C warm-water tail-flick test, N-CBM-TAMO given supraspinally acted as a short-term partial agonist. Only submaximal antinociception was observed at doses up to 100 nmol. Pretreatment of mice with i.c.v. N-CBM-TAMO at 10 nmol which exhibited moderate short-term antinociception produced a long-term antagonism of morphine-induced antinociception. In the mouse acetic acid writhing test, N-CBM-TAMO acted as a potent full κ agonist. These *in vivo* data are consistent with the *in vitro* binding data which demonstrated that incubation of bovine striatal membranes with N-CBM-TAMO resulted in wash-resistant inhibition of μ and κ opioid binding. Scatchard analysis of saturation binding data showed that N-CBM-TAMO decreazed the B_{max} value without affecting the K_d value for the μ-selective peptide [^{3}H]D-Ala^2,(Me)Phe^4,Gly(ol)^5]enkephalin (DAMGO). Whereas, N-CBM-TAMO increased the K_d value without altering the B_{max} value for the κ-selective ligand [^{3}H]U69,593. This study demonstrates that N-CBM-TAMO is a very potent κ agonist and at higher concentrations produces long-term antagonism of antinociception mediated by μ opioid receptors.

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CHARACTERIZATION OF ENDOGENOUS OPIOID/NEUROKININ PROCESSING OF NOCICEPTIVE STIMULI IN THE SPINAL CORD

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Neurokinin (NK) 1, 2 and 3 receptors are present in the dorsal horn of the spinal cord, the origin of ascending somatosensory pain pathways. Substance P, NKA. and NKB have the highest affinity for NK1, NK2, and NK3 receptors, respectively. We evaluated a paradoxical situation observed following NK administration. Pharmacological doses of intrathecally administered NK agonists produced antinociception in the PPQ test, an effect which was blocked by naloxone, indicating that the NK agonists may release endogenous opioids.
tested [ED50's (± C.L.'s) in μg/mouse] included: NK1 agonist, GR73632 [20 (12 -33)]; NK2 agonist GR 64349 [1μg =80% inhibition)]; NK3 agonist (Pro7)NKB[7 (0.9-53)]. NK antagonists also produced antinociception in the PPQ test, but were not blocked by naloxone. Drugs tested [ED50's ± C.L.'s in μg/mouse] included: NK1 antagonist GR82334 [33 (20-55)]; NK2 antagonist MEN10,376 [9.8 (7-14)]; NK3 antagonist {trp7β-ala8}NKA [24 (13-43)]. NK agonists and antagonists may act predominantly at two different sites in their interaction with opioids. Pharmacological doses of the NK agonists may act predominantly at NK receptors on opioid neurons, release endogenous opioids and induce antinociception, while pharmacological doses of NK antagonists may produce antinociception predominantly by interaction with NK receptors on dorsal horn neurons, reducing the nociception produced by tonically released NK's.

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INHIBITION OF SUPRASPINAL SUBSTANCE P (SP) ANALGESIA BY SELECTIVE OPIOID RECEPTOR ANTAGONISTS

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We have reported that noxious cold results in an increased release of SP from the periaqueductal gray (PAG) of rats. SP microinjection into the PAG produces analgesia which can be reversed **by** naloxone, although SP does not bind to opioid receptors, suggesting that it may be affecting the opioid system indirectly. Our results also showed that release of ß-endoqhin (P-E) from the PAG is increased by SP, indicating that the SP analgesic effect is related to B-E release. In the present study, we used selective opioid receptor antagonists to determine which type of opioid receptor is involved in the SP-induced analgesia. A stainless steel guide cannula was implanted unilaterally into the PAG of male S-D rats. The percent maximum possible analgesia (% MPA) was determined by the cold water (-3 °C) tail-flick test. The μ opioid receptor antagonist CTAP, κ opioid receptor antagonist nor-BNI, δ opioid receptor antagonist naltrindole (NTI),ε/μ/δ opioid receptor antagonist ß-E1-27 or SP antagonist WIN 51,708 (WIN), were microinjected into the PAG 15 min before SP microinjection into the same region. IntraPAG microinjection of SP (1.5-3 nmol) alone produced analgesia with the peak response (40-60 % MPA) at 45 minutes. The effect can be blocked by pretreatment with WIN (2.5 nmol). The analgesia caused by SP (1.5 nmol) was attenuated by pretreatment with CTAP (0.3 nmol) or ß-E1-27 (1 nmol) and completely blocked by CTAP (0.9 nmol) or ß-E1-27 (1.6 nmol). SP-induced analgesia was reduced slightly, but not significantly, by pretreatment with NTI (1 nmol) or nor-BNI (1.2 nmol). B-E (0.5 nmol) microinjected into the PAG produced analgesia and it was blocked by pretreatment with CTAP or ß-E1-27. These data provide further evidence that intraPAG-SP-induced analgesia involves activation of the μ opioid receptor within this region and that supraspinal SP released during noxious cold interacts with the endogenous opioid network, most likely by releasing O-E, to produce analgesia through the μ opioid receptor.

ACKNOWLEDGEMENTS: Supported by NIDA grant DA 00376.

CHOLECYSTOKININ-INDUCED STIMULATION AND INHIBITION OF MORPHINE ANTINOCICEPTION

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Although recent reports describe cholecystokinin (CCK) as an endogenous anti-opioid, we find it produces both stimulation and inhibition of morphine antinociception. CCK-opioid interactions were evaluated in the mouse hot plate assay, following simultaneous i.c.v. administration of morphine (0.1-3.0 mg), CCK (0.3 mg), or morphine + CCK. In 6 of 11 experiments, CCK significantly increased morphine antinociception, resulting in a 3-fold shift to the left in the morphine dose-response curve. In 5 of 11 experiments, CCK significantly decreaised morphine antinociception, resulting in a 3-fold shift to the right. When CCK increased morphine antinociception, CCK alone had a signilicantly greater antinociceptive effect (35.5 (3.2) than when CCK inhibited morphine antinociceplion (19.3 (4.8). These results suggest that the modulatory effects of CCK on morphine can either be stimulatory or inhibitory, and the direction of modulation depends on the intrinsic antinociception associated with CCK itself.

ACKNOWLEDGEMENTS:

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THE AMPA RECEPTOR ANTAGONIST, LY293558, ATTENUATES MU BUT NOT KAPPA. OPIOID ANALGESIC TOLERANCE

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Competitive (LY274614) and noncompetitive (MK801 and dextromethorphan) NMDA receptor antagonists attenuate or reverse morphine (MOR) but not U50488H (U50) tolerance (Inturrisi, Reg. Pept. 54: 129-130, 1994). Like NMDA antagonists, the systemically active, competitive AMPA receptor antagonist, LY293558, has anticonvulsant and neuroprotective properties. To determine whether AMPA receptors modulate tolerance, LY293558 (LY) (by tid, sc injection or by continuous sc infusion using a minipump) was coadministered with increasing doses of MOR or U50 (sc, tid at 10, 20 and 40 mg/kg per day) or saline. The MOR tail-flick ED50 in CD-1 mice on day four increased from 4.3 mg/kg to 10.5 mg/kg. LY at 10 mg/kg sc did not alter MOR tolerance while the 45 or 60 mg/kg/24h sc infusion attenuated MOR tolerance (ED50 values were 5.4 mg/kg and 5.6 mg/kg, respectively). The U50 ED50 increased from 7.5 mg/kg to 52.4 mg/kg, on day four and LY infusion at 60 mg/kg/24h sc failed to alter this value. These doses of LY do not alter morphine or U50 ED50 values, or motor performance. AMPA receptor activation may contribute 10 MOR (mu) but not U50 ($kappa_1$) opioid analgesic tolerance.

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DYNORPHIN A (1-13): BIOTRANSFORMATION IN HUMAN AND RHESUS MONKEY BLOOD AND ANTINOCICEPTION

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The degradation of dynorphin A (1-13) (DYN A 1-13) in rhesus monkey and human blood was studied with matrix-assisted laser desorption/ionization mass spectrometry (*e.g.,* Chou *et. al.,* 1994). This allows identification of biotransformation products after DYN A 1-13 addition (0.59 mg/ml) to freshly drawn blood (37" C, n=3, *in vitro* model), and in monkeys, after intravenous injection of DYN A 1-13 (32 mg/kg, *in vivo* model). In the *in vitro* model, DYN A 1-13 was rapidly processed to DYN A 1-12, which survived for approximately 15 minutes (rhesus monkey blood) or 30 minutes (human blood), with a gradual increase in DYN A 2-12 over those periods. The only other opioid fragment observed was DYN A 1-6 (rhesus monkey blood only). The DYN A 2-13 fragment was not detected at any timepoint. Initial studies using the *in vivo* model reveal a similar profile, but with faster biotransformation of all fragments. DYN A (1-13) thermal antinociception is dose-dependent (0.32-3.2 mg/kg, i.v.), begins within 15 minutes after administration, and lasts for approximately 30-45 minutes (at the highest dose, 3.2 mg/kg, i.v.). There would be no opioid fragments detectable in plasma under the latter conditions.

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Chou, J. Z., Kreek, M. J. and Chait, B. T. Matrix-assisted laser desorption mass spectrometry of biotransformation products of dynorphin A in vitro. J Am Soc Mass Spectrom 5:10-16, 1994.

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ANTINOCICEPTIVE EFFECTS OF COCAINE ALONE AND IN COMBINATION WITH OPIATES IN RHESUS MONKEYS

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This study characterized the antinociceptive effects of cocaine alone and in combination with mu, delta, and kappa opioids in rhesus monkeys. The shaved tails of four rhesus monkeys were exposed to warm water (42-58°C), and tail withdrawal latencies (20 sec maximum) from each temperature were determined. The temperature that produced a tail withdrawal latency of 10 seconds (T10) was interpolated, and drug-induced changes in the T10 value (ΔT10) were calculated. Dose-dependent increases in ΔT10 were produced by cumulative doses of cocaine (0.032-1.8 mg/kg); the *mu* agonists fentanyl (0.001-0.1 mg/kg), morphine (0.1-18 mg/kg) and nalbuphine (1-32 mg/kg); and the kappa agonist U69,593 (0.0032-0.1 mg/kg). The delta agonist BW373U86 (0.56 mg/kg) produced no effect. Relative antinociceptive efficacies, determined from the maximum ΔT10 values produced by each drug, were fentanyl≥U69,593>morphine≥nalbuphin>cocaine>BW373U86. Time courses of single dose combinations of cocaine (0.1-1.8 mg/kg) and morphine (0.32-10.0 mg/kg) usually produced additive effects similar to the sum of the effect of cocaine alone plus the effect of morphine alone. The highest dose of cocaine (1.8 mg/kg) in combination with the lowest dose of morphine (0.32 mg/kg) produced effects greater than additivity. In addition, superadditive effects were consistently observed at the 90 minute timepoint across doses, although cocaine when administered alone produces no aminociceptive effects after 90 minutes. Cocaine (1.8 mg/kg) was also combined with the nalbuphine (1.0, 10 mg/kg), fentanyl (0.001, 0.032 mg/kg), the BW373U86 (0.56 mg/kg) and agonist U69.593 (0.0032, 0.032 mg/kg). Cocaine had little or no *effect* on fentanyl and BW373U86, a superadditive effect on nalbuphine, and cocainc/U69,593 combinations were less effective than either drug alone. These findings suggest that the effect of cocaine on opioid combinations may depend on the efficacy and receptor selectivity or the opioid agonist.

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IMMUNOGENS FOR THE GENERATION OF ANTIBODIES TO CATALYZE COCAINE HYDROLYSIS

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An agent that would facilitate the breakdown of cocaine in blood to less active products would reduce psychoactive effects, diminish reinforcing properties, and thereby facilitate treatment of cocaine abuse with other therapeutic modalities. Because they can be designed to carry out a specific reaction with high substrate selectivity, catalytic antibodies are promising agents for this purpose. In this paper we describe the design and synthesis of transition state analogs (TSAs) for the hydrolysis of cocaine to ecgonine methyl ester. These analogs were conjugated to protein, the resulting conjugates were used to immunize mice and hybridomas producing antibodies capable of binding the TSA were produced by standard techniques. Monoclonal antibodies were produced in ascites and purified by ammonium sulfate precipitation and protein A isolation. Two of these antibodies gave definite, but quite modest, catalysis of cocaine hydrolysis. This was demonstrated by enhanced production of benzoic acid from cocaine in the presence of antibody, which was abolished by the addition of transition state analog to the reaction.

ACKNOWLEDGEMENTS:

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SEARCHING FOR COCAINE ANTAGONISTS. SAR STUDIES OF AROMATIC RING SUBSTITUTED METHYLPHENIDATE ANALOGS

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The use of cocaine and other stimulants is a continuing problem in the United States. An important site of the molecular action of these drugs is the binding site associated with the dopamine transport complex. We are currently involved in a long term program to develop antagonists for these agents. The aim of this work to make drugs which will selectively bind to the transporter without diminishing its function. A large number of aromatic ring substituted (±)-three methylphenidate (ritalin) derivative have been synthesized and evaluated for inhibition of [^{3}H]WIN 35,428 binding and [^{3}H]dopamine uptake and in various animal behavioral tests. Compared to unsubstituted methylphenidate the 4-substituted compounds were generally as potent or more potent, the 3-substituted compounds were either more potent (electron withdrawing) or less potent (electron releasing) and the 2-substituted compounds much less potent (ca. 100-1000 fold). Analysis of the *in vitro* data by looking at the ratio of inhibition uptake to binding indicated that the 4-substituted compounds might have a greater potential as possible cocaine antagonists. Preliminary results in some of the animal models were encouraging. The synthesis and pharmacology of compounds will be discussed in detail.

SAR OF DIFLUOROPINE: A POTENT AND SELECTIVE LIGAND FOR THE DOPAMINE TRANSPORTER

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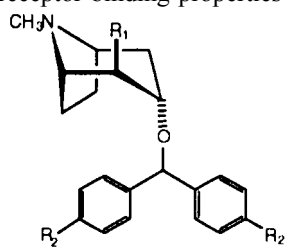
The reinforcing properties and stimulant effects of cocaine are associated with its binding to the dopamine transporter. While structure activity relationship studies of cocaine analogs had indicated that binding is stereoselective and that only the *R*-enantiomers were active in a wide variety of measures, we recently reported that the S-enantiomer, difluoropine, binds with high affinity and selectivity. We now report the synthesis and receptor binding properties of analogs of difluoropine.



Benztropines

	R_1	R_2
5a:Difluoropine	β-$COOCH_3$	F

The target compounds were prepared by total synthesis from 3-tropinone. The binding data for these compounds show that introduction of larger R_2 groups reduces potency. Also, it was shown that sreric bulk can be tolerated at the nitrogen site. A comparison of binding data for the tropanes, GBR analogs, and 2-carbomethoxybenztropines, indicated that the benztropines may be more GBR-like in their mode of binding to the DAT than they are tropane-like. This conclusion supports the notion that the binding site for cocaine may be different from that for the benztropine or GBR analogs. This difference may be exploited for the discovery of a cocaine antagonist.

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SYNTHESIS AND LIGAND BINDING OF RIGID ANALOGS OF PAROXETINE

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Different configurational isomers of N-nor-3-(4'-fluorophenyl)-2-[(3",4"-methylenedioxyphenyl)hydroxymethylltropane (**1**) have been designed and synthesized which are structurally similar to paroxetine (**2**), a potent serotonin uptake inhibitor. Both the tropane analogs and paroxetine contain a piperidine ring with an aryl and an oxygenated carbon moiety in similar positions on the heterocyclic ring. The major structural difference hetween the two is the tropane analogs possess an ethylene bridge, not present in paroxetine, which lends a conformational rigidity to the piperidine ring. The preparation and biological evaluation of these compounds provide new information concerning the structural features required for potent and selective biding to the cocaine binding site on the serotonin transporter. Since cocaine's action at serotonin transporters appears to modulate self-administration, it is important to identify those compounds which may he useful in medication development for the treatment of drug abuse. Six of the possible eight stereoisomers of the tropane analogs of paroxetine have been prepared. Inhibition of radioligand binding for those compounds at the dopamine (DA), serotonin (5HT), and norepinephrine (NE) transporters shows that the 2b,3a-isomer of **1** derived from (-)-cocaine has good affinity for the 5-HT transporter. The 2b,3a-isomer of **1** derived from (-)-cocaine and its N-methyl analog **5a** both have good affinity for the DA transporter. Surprisingly, the 2b,3b-isomer derived from (-)-cocaine and its N-methyl analog **5b** showed low affinity for the DA transporter. This data suggests that these tropane analogs of paroxetine may be binding to the DA transporter in a way different from 3b-(4-fluorophenyl)tropane-2b-carboxylic acid methyl ester (WIN 35,428).

ACKNOWLEDGEMENTS:

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HETEROCYCLIC GBR 12909 ANALOGS AS POTENTIAL COCAINE ABUSE TREATMENT AGENTS

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LMC, NIDDK, NIH, Bethesda, MD; LCR, ARC, NIDA, Baltimore, MD; MDD, NIDA, Rockville, MD; BPB, NIMH, NIH, Bethesda, MD; Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland; RTI, Research Triangle Park, NC

Cocaine is among the most widely abused and strongly reinforcing drugs known. Our approach to treatment and prevention of cocaine abuse involves development of high affinity, slowly dissociating, low intrinsic activity cocaine receptor agonists. *In vivo* microdialysis studies of extracellular dopamine (ECDA) levels in the rat striatum showed that the lead compound GBR 12909 blocked most of the large elevation of ECDA produced by cocaine but when administered alone only produced modest increases in ECDA. Recent studies in monkeys trained to self-administer cocaine with GBR 12909 and some of its analogs have shown that it is possible to prevent cocaine self-administration with little effect on "normal behavior" as measured by food intake. Heterocyclic GBR 12909 analogs synthesized in our program exhibit high affinity for binding to the DA transporter and most of them are potent and selective inhibitors of DA reuptake in both striatum and nucleus accumbens. Interestingly, the pyridine derivatives of GBR 12909 are the most selective DA transporter ligands, whereas the quinoline analogs exhibit good affinity at both DA and serotonin (5HT) sites. In tissues obtained from rats chronically treated with cocaine, the IC_{50} values for some of the new analogs were significantly lower than in control rats. Additionally, new congeners show profiles similar to GBR 12909 *in vivo e.g.,* stimulate the locomotor activity in rats following i.p. injection and suppress the cocaine-maintained responding in rhesus monkeys trained to self-administer cocaine. These results suggest that new agents, heterocyclic GBR 12909 analogs, may be useful for the treatment and prevention of human cocaine abuse.

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MAZINDOL ANALOGS AS POTENTIAL INHIBITORS OF THE COCAINE BINDING SITE. STRUCTURE ACTIVITY RELATIONSHIPS

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Mazindol (5-(4-chlorophenyl)-2,3-dihydro-5H-imidazo[2,1-a]isoindol-5-o1), a potent inhibitor of cocaine binding at the dopamine transporter in the rat striatum, when administered orally to cocaine abusers in an open clinical study significantly reduced cocaine craving and use. In order to determine the structural features of mazindol that are important for binding a series of analogs that contain a wide range of substituents and various heterocyclic systems have been prepared. The inhibition of [^{3}H] WIN 35,428 binding and [^{3}H] dopamine uptake in rat striatal tissue for these compounds will he presented. In addition, a putative pharmacophore model comparing mazindol and R-cocaine will also be proposed.

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SYNTHESIS AND BIOLOGICAL EVALUATION OF PIPERAZINE DERIVATIVES AS POTENTIAL DOPAMINE REUPTAKE INHIBITORS

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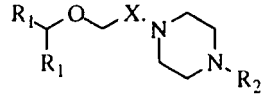
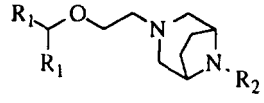
Recent studies have shown that cocaine hinds with high affinity to the dopamine transporter and inhibits dopamine reuptake into the presynaptic neuron. The resulting elevation of the extracellular concentration of dopamine (ECDA) is believed to result in its euphoric and addictive effects. GBR 12935 and GBR 12909 have been shown to possess high affinity and selectivity, but a slow dissociation rate and low intrinsic agonist activity for the dopamine transporter. Their partial agonist effects on ECDA levels and non-stimulant profile in humans have led us to study their potential use as therapeutic agents for cocaine abuse. We have synthesized a series of GBR analogs (**I, II**) to study their binding and DA uptake activities. The binding data of DA and 5-HT transporters (labeled with [^{125}I]RTI-55) show that the Spiro compound in series **I** (X=CH_2, R,=*p* -fluorophenyl, R_1=spiro portion of spiperone) displays high affinity at the DA transporter sites, however low selectivity over 5-HT transporter binding. The bridged piperazines (II), which were designed to mimic the structure of cocaine, present high to moderate potency at DA transporter. The N-methyl compound (R,=phenyl, R,=methyl) shows the highest selectivity (IC_{50}(DA)=83.3 nM, IC_{50}(5-HT)=9334 nM, 5-HT/DA=112), while its *p*-fluorophenyl derivative possesses the highest potency (IC_{50}(DA)=7.98 nM, IC_{50}(5-HT)=705 nM, 5-HT/DA=88) at DA transporter sites. Consistent with the observation from earlier SAR studies, the compounds with *p*-fluoro function tend to increase DA transporter binding and decrease the selectivity over 5-HT sites.



I (X=carbonyl or CH_2)



II

NOVEL 2'-AND-3'-SUBSTITUTED-3α-DIPHENYLMETHOXYTROPANE ANALOGS PROVIDE ADDITIONAL SAR AT THE DOPAMINE TRANSPORTER

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Preparation of a series of 4'- and 4',4"-substituted-3-α-diphenylmethoxy-1αH,5αH-tropane analogs has resulted in selective, high affinity probes for the dopamine transporter (DAT). The structure-activity relationships (SAR) in this series suggest an important role of aromatic ring substitution for both the potency and selectivity of these compounds. To further explore the effect of various aromatic ring substitution patterns, analogs were prepared containing meta and ortho phenyl ring substituents. The compounds synthesized were tested for inhibition of [^{3}H]WIN 35,428 binding and [^{3}H]dopamine (DA) uptake at the DAT. 3'-Chloro-3α-diphenylmethoxytropane (3'-Cl, 4c) displaced WIN 35,428 binding (K_i = 22 nM) more potently than either cocaine or benztropine (BZT, K_i = 118 nM), and was equipotent to the 4'-Cl analog. Interestingly, compound 4c was less potent than 4'-Cl analog in inhibiting DA uptake, suggesting that these compounds may give some clues to separabiligy of binding and inhibition of uptake at the DAT. Surprisingly, this compound generalized to the cocaine cue in animals trained to discriminate 10 mg/kg cocaine from saline, while 4'-Cl BZT did not. Other SAR indicted by this series of compounds included the finding that meta substituted electron withdrawing groups were not preferable, but that the steric bulk of these substituents was tolerated much better in this position than in the para position. Ortho aromatic substitution also was not favorable. This loss of potency may be due to the ortho groups preventing the rotation of one of the phenyl rings in the diphenylmethoxy moiety thus not allowing the ring to occupy the orientation necessary for optimum binding. These findings provide additional SAR at the DAT and may enable the development of novel cocaine therapeutics.

EXCITATORY AMINO ACID ANTAGONISTS ATTENUATE COCAINE-INDUCED INCREASES IN EXTRACELLULAR DOPAMINE

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There is increasing evidence that excitatory amino acid (EAA) antagonists of the NMDA and non-NMDA subtypes can block cocaine-induced behavioral activation and/or the reward value of self-administered cocaine. These indications from behavioral studies led us to examine the impact of EAA receptor inhibition on the ability of systemic cocaine to elevate extracellular DA. The AMPA/Kainate-receptor subtype antagonist CNQX, and NMDA receptor antagonists, AP-5 and MK-801, were infused via a microdialysis probe placed in the nucleus accumbens. The local infusion of AP-5 (500 μM), MK-801 (50 μM), and CNQX (100 μM), started 80 minutes prior to cocaine injection (15 mg/kg, i.p.), significantly inhibited the cocaine-induced increase in extracellular DA; the increase resulting from 7.5 mg/kg cocaine was completely blocked by the 100 μM CNQX pretreatment. Simultaneous infusion of 500 μM AP-5 and 100 μM CNQX did not lead to further reductions in the effects of cocaine when compared to either antagonist alone. Systemic pretreatment with the AMPA subtype antagonist NBQX (10 mg/kg i.p., 15 min prior to cocaine) also significantly reduced the ability of cocaine (15 mg/kg, i.p.). to elevate extracellular DA. Our results suggest that both NMDA and AMPA/Kainate subtypes of EAA receptors may contribute to the stimulatory effect of cocaine on extracellular dopamine in the nucleus accumbens, and support suggestions for the development of these classes of drugs for therapies aimed at reducing the reinforcing effects of psychostimulants.

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NEUROADAPTIVE REGULATION OF THE D3 DOPAMINE RECEPTOR BY COCAINE

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Chronic cocaine abuse increases dopamine neurotransmission by blocking dopamine uptake and activating dopamine receptor subtypes. We have used [^{3}H]-(+)-70H-DPAT in the presence of $MgC1_2$ and guanine nucleotides to selectively map and characterize the D3 receptor postmortem in the human brain from cocaine overdose deaths. *In vitro* autoradiography of [^{3}H]-(+)-70H-DPAT binding demonstrated that D3 receptors were markedly elevated over the limbic sectors of the striatum. Equilibrium binding assays confirmed that there were no alterations in the affinity of the D3 receptor for [^{3}H]-(+)-70H-DPAT. D3 receptor densities were elevated over the medial divisions of the substantia nigra and in the ventral tegmental area from cocaine overdose victims. The localization of D3 receptors in the human substantia nigra suggests that this subtype may function also as a somatodendritic autoreceptor. The expression of D3 receptor mRNAs was studied in parallel with ligand binding assays. Preliminary results using RT-PCR revealed differential gene expression of D3 mRNAs in the nucleus accumbens of the cocaine overdose and excited delirium victims. Both alternative spliced variants of the D3 gene, D3 and D3nf mRNA were detected in the nucleus accumbens of the drug-free control subjects. The D3nf mRNA represented 33 ± 5% of the total D3 mRNA present. The relative abundance of the D3 mRNA was increased by 23 ± 4% in the cocaine overdose victims and reduced by 28 ± 5% in the excited delirium subgroup relative to control values. The D3nf mRNA was reduced by 12 ± 3% in the excited delirium subgroup, whereas none was detectable in the cocaine overdose victims. The results suggest a role for mesolimbic dopamine acting at the D3 receptor subtype in the brain's reward circuitry. The D3 receptor subtype may prove to be useful target for drug development of anti-cocaine medications.

ACKNOWLEDGEMENTS: Supported by NIDA grant DA-06227.

DEXTROMETHORPHAN AND SELECTED ANALOGS HAVE HIGH AFFINITY FOR THE RAT SEROTONIN TRANSPORTER

C. M. Dersch; J. S. Partilla; B. Emilien; K. C. Rice; A. H. Newman; J. H. Shah; F. I. Carroll; and R. B. Rothman

CPS and PBS, DIH, NIDA, NIH, Baltimore MD; LMC, NIDDK, NIH, Bethesda, MD; Research Triangle Institute, Research Triangle Park, NC

The unnatural (+)-enantiomers of the opiates, which generally have very low affinity for opioid receptors, bind with high affinity to several CNS sites/receptors including sigma binding sites, the PCP site associated with the NMDA-receptor complex (the PCP receptor) and dextromethorphan binding sites. The present study determined the K_i values of dextromethorphan (DM) and several analogs at the rat caudate 5-HT transporter (SERT) labeled with [^{125}I]RTI-55 (0.01 nM). To assay the SERT, striatal membranes were incubated for two to four hours at 25° C in 55.2 mM sodium phosphate buffer, pH 7.4, containing protease inhibitors, anti-oxidants and 100 nM GBR12935 to block [^{125}I]RTI-55 binding to the DA transporter (DAT). The K_i values of fluoxetine, DM, AHN1-048 (3-O-ethoxy-N-methylmorphinan), dextrallorphan, thebaine, cammiphen and (+)-pentazocine were: 31 nM, 62 nM, 80 nM, > 1 μM, > 1 μM. > 1 μM, > 1 μM. These data identify a new high affinity binding site for DM.

PCP SITE 2 AND THE COCAINE BINDING SITE OF THE DA TRANSPORTER ARE NOT ALTERNATE CONFORMATIONS OF THE SAME BINDING SITE

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Several lines of evidence suggest that the PCP analog [^{3}H]TCP labels a high affinity MK801-insensitive binding site (PCP site 2) which is associated with the biogenic amine transporter (BAT) system. This study tested the hypothesis that PCP site 2 and the cocaine binding site of the DA transporter (DAT) (labeled with [^{125}I]RTI-55) are alternate conformations of the same binding site. [^{3}H]TCP and [^{125}1]RTI-55 assays were conducted using guinea pig brain membranes under two assay conditions: 1) PCP site 2 conditions - 18-24 hour incubations at 4° C in 5 mM Tris-HCl, pH 8.0 in the presence of 500 nM (+)-MK801 and 2) BAT assay conditions - 18-24 hour incubations at 4° C in 55.2 mM sodium phosphate buffer, pH 7.4 in the presence of 50 nM paroxetine. A direct prediction of the above hypothesis is that under PCP site conditions [^{125}I]RTI-55 should label a site with the characteristics of PCP site 2, and that under BAT conditions [^{3}H]TCP should label a site with the characteristics of the DAT. The IC_{50} values of RTI-55 and selective PCP site 2 compounds (TCP, (+)- and (-)-RTI-41) were therefore determined using both radioligands under both assay conditions. The results were not in accord with this prediction. We conclude that PCP site 2 and the cocaine site of the DAT are not alternate conformations of the same site.

CHARACTERIZATION OF A NOVEL COCAINE BINDING SITE (SERTsite2) IDENTIFIED WITH [125I]RTI-55 UNDER SEROTONIN TRANSPORTER ASSAY CONDITIONS IN MEMBRANES PREPARED FROM HUMAN, MONKEY AND GUINEA PIG CAUDATE

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[^{125}I]RTI-55 is a cocaine analog with high affinity for the DA and 5-HT transporters. We characterized non-DA-transporter associated [^{125}I]RTI-55 binding sites in human, monkey and guinea pig caudate membranes. The assay conditions were: 18 - 24 hour incubations at 4¤ C in 55.2 mM sodium phosphate buffer, pH 7.4, plus 100 nM GBR12935 to block binding to the DA transporter (DAT). Under these conditions no specific binding was detectable using CHO cells stably expressing the human DAT. Two sites were readily resolved. The Ki values (nM) of representative test agents (monkey caudate) are:

Drug	SERT	$SERT_{site2}$	Rat DAT
Paroxetine	0.074	2436	876
RTI-55	0.17	2.60	0.76
lndatraline	2.7	8.7	1.75
Citralopram	1.40	46358	17783
Cocaine	137	1176	341
RTI-120	1577	26.7	12.7
BTCP	79	314	5.0
Mazindol	82	1820	37.6

Other studies demonstrate that SERTsite2 also occurs in human caudate-putamen and cortex (see Ohuoha *et. al.,* this volume). These studies demonstrate the existence of an [^{125}I]RTI-55 binding site (SERTsite2) with a novel ligand-selectivity profile.

NEUROCHEMICAL LESIONS DISTINGUISH MULTIPLE COCAINE BINDING SITES IN RAT BRAIN LABELED BY [^{125}I]RTI-55

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[^{125}I]RTI-55 is a cocaine analog with high affinity for the DA and 5-HT transporters (DAT and SERT). Recent studies in our lab identified two additional binding sites labeled by [^{125}I]RTI-55: "DAT_{site2}" labeled under DAT assay conditions (*i.e.,* with 50 nM paroxetine as a blocker) and "$SERT_{site2}$" labeled under SERT assay conditions (*i.e.,* with 100 nM GBR12935 as a blocker). $SERT_{site2}$ is not detectable in rat brain. Thus, the present study determined the effects of neurochemical lesions on [^{125}I]RTI-55 binding to DAT, DAT_{site2} and SERT. In some cases NE transporters were labeled with [^{3}H]nisoxetine. Neurochemical lesions were produced by administration of 6-OH-DA (i.c.v., DA nerves), 5,7-DHT (i.c.v., 5-HT nerves), (+)-fenfluramine (sc, 5-HT nerves), reserpine (i.p., amine storage granules) and DSP (ip, NE nerves). The results of this study include the following findings. **1)** Cos cells transiently expressing the cloned rat DAT do not express DAT_{site2}. 2) In rat non-caudate, non-hippocampal brain regions 5,7-DHT and fenfluramine-induced lesions reduce SERT, but not DAT and DAT_{site2}; 6-OH-DA-induced lesion equally reduces DAT and DAT_{site2} but not SERT; DSP-4- and reserpine-induced lesions are without effect ml SERT, DAT and DAT_{site2} and DSP-4 lesions reduce [^{3}H]nisoxetine binding by 90%. 3) In rat hippocampus, Fenfluramine-induced lesions reduce SERT, but not DAT and DAT_{site2}; 5,7-DHT-induced lesions reduce SERT, DAT but not DAT_{site2}; 6-OH-DA- and 5,7-DHT-induced lesions reduce DAT more than DAT_{site2}. These data support the hypothesis that DAT_{site2} is localized to DAergic nerves, is not localized to storage granules, and is distinct from the classic DA transporter (DAT).

QUANTITATIVE AUTORADIOGRAPHY OF A NOVEL COCAINE BINDING SITE (SERTsite2) IN HUMAN BASAL GANGLIA

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One working hypothesis that explains the chronic effects of cocaine use in humans is that its chronic use leads to functional DA and 5-HT deficits. Double-blind placebo-controlled clinical studies using DA and 5-HT reuptake inhibitors have generally yielded equivocal results. One possible explanation for these disappointing findings may be that sites other than the classical DA (DAT) and 5-HT (SERT) reuptake sites may be involved in the maintenance of cocaine addiction in humans. We report here the localization in human basal ganglia of a novel cocaine binding site (SERTsite2) labeled using [125I]RTI-55 under SERT assay conditions (blocker = 5000 nM benztropine {BZ}). Paroxetine {PX} has high affinity for the classical SERT (Ki= 0.149 nM) but lower affinity for SERTsite2 (Ki= 1354 nM). Thus 50 nM of PX was used to block [125I]RTI-55 binding to SERT permitting the selective visualization of SERTsite2. Slides were preincubated for 30 minutes in 55.2 mM sodium phosphate buffer containing 50 nM PX and 5000 nM BZ, and then incubated for four hours at 4¤C in phosphate buffer, containing 0.01 nM [^{125}I]RTI-55, 5000 nM BZ and 50 nM PX. Nonspecific binding was assessed using 10 µM GBR12909. Classical SERT binding was determined using 2 nM [3H]citalopram. Binding quantification was performed with a Macintosh computer image system. Analysis of the autoradiograms show binding of SERTsite2 in the human basal ganglia. The distribution of SERTsite2 is different from the distribution of the classical serotonin uptake sites in the human basal ganglia. Whereas the distribution of the classical seroronin uptake sites indicates binding density in the accumbens > putamen > caudate, the density of SERTsite2 binding sites is distributed as putamen > caudate> accumbens. This difference lends support to the notion that SERTsite2 is a different site than the classical serotonin reuptake site. The binding and pharmacological properties of SERTsite2 is presently being investigated.

COCAINE UPREGULATES KAPPA OPIOID RECEPTORS IN HUMAN STRIATUM

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Cocaine dependence may result from the dysregulation of a number of distinct yet interacting neurochemical systems which act in concert. Endogenous opioids acting at mu and kappa receptors modulate dopamine neurotransmission. Recent studies demonstrate that administration of kappa agonists prevents the development of sensitization to the rewarding effects of cocaine (Nadaar, 1995). These findings suggest that cross-talk between opioids and dopamine may lead to a sequence of neuroadaptive changes that contribute to the development of sensitization, tolerance and dependence. In the present study, quantitative *in vitro* autoradiography with the opioid antagonist [^{125}I]IOXY was used to assess the status of the kappa-receptor postmortem in the human brain from cocaine overdose deaths. The kappa receptor was selectively labeled with [^{125}I]IOXY on half-hemisphere coronal slide-mounted tissue sections pretreated with the site-directed acylating agents BIT (mu-selective) and FIT (delta-selective). Compared to drug-free and age-matched control subjects, the cocaine overdose victims exhibited a higher density of [^{125}I]IOXY labeling over the ventral sectors of the anterior striatum, nucleus accumbens and in the anterior cingulate cortex (Brodmann area 24). These results demonstrate that chronic cocaine abuse leads to regulatory changes in the density of kappa receptors over discrete loci in brain. Since kappa receptor agonists have been shown to inhibit mesolimbic dopamine neurotransmission, the present results suggest that neuroadaptive regulation of kappa receptors may occur in response to increased levels of intrasynaptic dopamine. Compensatory increases in striatal and corticolimbic kappa receptor numbers may underlie some of the psychological and physiological effects associated with the appearance of cocaine sensitization and withdrawal distress.

THE CARDIOVASCULAR EFFECTS OF SELF-ADMINISTERED COCAINE IN RATS

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Studies examining cocaine's (COC) cardiovascular effects have used models involving experimenter controlled drug administration. In this study arterial pressure (AP) and heart rate (HR) were recorded in rats during periods of COC self-administration. The jugular vein and femoral artery were catheterized for the administration of drugs and recording of AP, respectively. HR was determined from the AP signal. In one-hour sessions, rats (n=5) were allowed up to 20 infusions of COC (0.25 mg/kg/infusion) on a CRF schedule, with a 30-s time out period after each infusion during which responses had no scheduled consequence. On the first day that rats received 20 infusions of COC, the first infusion significantly increased AP and HR (43±7 mmHg and 81±16 bpm). By the 20th infusion, COC no longer increased AP or HR (-2±6 mmHg and -1±1 bpm). Between the 1st and 20th infusions baseline AP was not changed (108±2 and 108±5 mmHg, respectively); however, baseline HR was significantly reduced between the 1st to the 20th infusions (377±11 bpm to 332±17 bpm). In a separate group of pentobarbital-anesthetized rats (n=4), 20 infusions of COC (0.25 mg/kg/infusion) were administered, one every two minutes. The first infusion of COC significantly increased AP (24±4 mmHg) and decreased splanchnic sympathetic nerve discharge (SND; -23±6 %). After infusion #20, SND and AP were significantly decreased as compared to the first infusion (-73±4 % and 6±1 mmHg). These data show that repeated self-administration of COC 1) decreased the magnitude of the AP and HR responses, 2) did not increase baseline AP, and 3) decreased baseline HR. In anesthetized rats, repeated administration of COC progressively decreased SND and the magnitude of the AP response. Thus, the decrease in cardiovascular responsiveness in conscious rats during self-administration of COC may be due to a progressive inhibition of SND.

A NOVEL PHARMACODYNAMIC ACTION OF COCAINE: CARDIOVASCULAR AND BEHAVIORAL EVIDENCE

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Intravenous cocaine (0.03-3 mg/kg) produced two distinct and temporally separable pharmacological effects in rats. One is an initial, large and brief increase in blood pressure (BP) and heart rate (HR) of a rapid onset. A rapid, brief and intense behavioral arousal accompanied these rapid cardiovascular effects. The other effect of cocaine is a prolonged locomotor activation of a relatively slower onset. Prolonged increases in BP and HR accompanied this locomotor effect. Dopamine receptor antagonists, SCM 23390 (0.03 mg/kg) or eticlopride (0.03 mg/kg), although antagonized cocaine's locomotor and sustained cardiovascular effects, but did not alter its initial rapid cardiovascular and behavioral effects. Peripheral dopamine receptor antagonist, domperidone (0.3 mg/kg) did not alter cocaine's effects. Unlike cocaine, Nisoxetine (0.1-1 mg/kg), a norepineplnine-selective inhibitor, fluoxetiue (0.3-3 mg/kg), a serotonin-selective uptake inhibitor and lidocaine (0.3-3 mg/kg), a sodium channel blocker, produced neither behavioral nor cardiovascular effects that arc comparable to cocaine's effects. GBR 12909, a dopamine-selective uptake inhibitor, shared cocaine's delayed, but not its initial rapid, cardiovascular and behavioral effects. These effects of GBR 12909 were prevented by SCH 23390 and eticlopride, but not by domperidone. These results indicate that behavioral and cardiovascular effects of cocaine are intricately linked and two molecular mechanisms appear to mediate these effects. One is a dopamine-dependent while the other may be ii monoamine- or sodium channel-independent novel action. The former mediates cocaine's locomotor effect and the accompanying prolonged increases in BP and HR, while the latter mediates the initial brief behavioral arousal and the accompanying rapid cardiovascular effects.

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COMPARISON OF THE EFFECTS OF COCAINE AND LIDOCAINE ON CARDIOVASCULAR FUNCTION IN ANESTHETIZED RABBITS

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In anesthetized animals, the primary effect of cocaine on cardiovascular function is to decrease heart rate and blood pressure and to prolong the QRS interval. These results suggest that cocaine's local anesthetic function may predominate in these studies. Therefore, we investigated the effects of cocaine in anesthetized rabbits and compared them to lidocaine at an equimolar dose to the highest dose of cocaine tested. New Zealand White rabbits (2-3 kg, n=4) were anesthetized and prepared with arterial and venous catheters. Cocaine (0.1, 0.3 or 2.0 mg/kg) or lidocaine (1.6 mg/kg, n=7) were injected i.v. and cardiovascular parameters were monitored. The results are presented below as a percentage change from baseline, which was obtained just prior to the drug injection (*=P<.05 from baseline, Values are mean ± S.E.M.).

% Change in:	Coc. 0.1 mg/kg	Coc. 0.3 mg/kg	Coc. 2.0 mg/kg	Lido. 1.6 mg/kg
MBP(mm Hg)	2 ± 3	-11±7	-39 ± 7*	-31 ± 10
HR (beats/min)	-0 ± 4	-14±5	-32 ± 7*	-19 ± 11
ABF (ml/mm)	35±31	6 ± 5	-4 ± 4	14 ± 12
QRS (msec)	14±5	85 ± 16*	277 ± 81"	106 ± 32*

Cocaine produced clear dose-dependent decreases in mean arterial blood pressure (MBP) and heart rate (HR) and a clear prolongation of the QRS interval. No dose of cocaine produced any significant change in aortic blood flow (ABF). A dose of lidocaine that was equimolar to the 2.0 mg/kg dose of cocaine produced nearly identical effects. These results suggest that in anesthetized animals, the cardiovascular effects observed may be primarily due lo the local anesthelic action of cocaine.

PLASMA COCAINE CONCENTRATION AFTER ONE MONTH ADMINISTRATION OF THE ALKALOID

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Administration of 40 mg/kg/day of cocaine for 28 days to rats by means of intraperitoneal osmotic pumps is well tolerated though accompanied by ultrastructural lesion of myocardium (CPDD 1991 NIDA monograph 105). A similar protocole was used to assay plasma concentration of cocaine and benzoylecgonine (B.E.G.) in 15 rats administered the same amount of cocaine for four weeks. Three animals were sacrificed on day 2, 6, 13, 19, 28. Their blood was analyzed by HPLC for cocaine and benzoylecgonine:

Day		Cocaine		Benzoylecgonine (g/ml)	
	n	Mean	S.D.	Mean	S.D.
2	3	155	167	3366	486
6	3	784	95	3320	1029
13	3	1605	74	6257	624
19	3	3311	380	6095	646
28	3	3699	494	6863	1053

Increases in plasma concentration of cocaine and benzoylecgonine becomes significant on the thirteenth day. A significant correlation was observed between plasma cocaine and benzoylecgonine concentration and duration of cocaine exposure ($r = 0.94$, $p < 0.001$ and $r = 079$, $p<0.001$, respectively). Interruption of heavy cocaine abuse is also followed by urinary excretion of its main metabolite B.E.G. lasting several weeks. An interaction between cocaine in high concentration and its rate limited metabolizing enzymes could result in its accumulation in heart and brain which might affect cellular metabolism function and structure.

EFFECTS OF INTRA-ACCUMBENS SULPIRIDE ON COCAINE-INDUCED LOCOMOTION AND CPP

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The effects of intra-accumbens sulpiride on locomotion and conditioned place preference (CPP) produced by intravenous (IV) cocaine were investigated. Rats received three conditioning trials which consisted of 30-minute exposures to two distinctive compartments of a CPP chamber on consecutive days. On one day of the trial, rats received bilateral injections of sulpiride (0, 0.025, 0.1, or 0.4 µg/0.5 µl/side) into the nucleus accumbens (NAc). Fifteen minutes later, rats were placed into a compartment and immediately injected with cocaine (0 or 4.2 mg/kg, IV). On the alternate day, rats received sham intra-accumbnes injections and 15 minutes later were placed into the alternate compartment. Locomotion and stereotypies were measured during trial 1 and 3. CPP was measured 24 hours after trial 3. Following behavioral testing, receptors occupied by sulpiride were quantified. Prior to sacrificing the rats (105 min), they were injected with their respective dose of sulpiride. followed 15 minutes later by systemic injection of the irreversible antagonist EEDQ. Sections containing the NAc were labeled with ^{3}H-sulpiride and the resulting autoradiograms revealed receptors protected from EEDQ-induced inactivation by the sulpiride given in vivo (*i.e.,* receptors occupied by sulpiride). Cocaine-induced locomotion was dose-dependently attenuated by sulpiride. Cocaine-CPP, however, was not altered by any dose of sulpiride. Each dose of sulpiride produced significant protection of receptors in the NAc. The two highest doses also produced significant protection of receptors in the caudate putamen. These findings suggest that D2-like receptors in the NAc mediate cocaine-induced locomotion, but not CPP.

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SIGMA RECEPTORS AND LOCOMOTOR ACTIVITY FOLLOWING CHRONIC INTRAVENOUS COCAINE ADMINISTRATION

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The role of sigma receptors in the central nervous system has not been fully elucidated, yet sigma-selective compounds have been reported to block the behavioral stimulation observed with cocaine administration. These studies examined the effect of chronic i.v. cocaine (0.5, 1.0, 3.0 mg/kg) administration for 14 days on sigma receptor density in the striatum/nucleus accumbens and alterations in cocaine-induced locomotor activity. Male Sprague-Dawley rats implanted with an intravenous access port (Mactutus, *et. al.,* 1994) were randomly assigned to activity chambers and habituated during two 60 minute test sessions following injection of heparinized saline. Total, peripheral and central activity data were then collected at five minute intervals during the 60 minute alternate daily test sessions. Animals were sacrificed 24 hours after the last injection and the density of sigma receptors was determined using 10-15 nM [^{3}H]DTG. Sigma receptors in the striatum were significantly elevated in a dose-dependent fashion compared to saline values and were predicted by the initial five minutes of peripheral (thigmotaxic) activity across all test days. However, sigma receptor density in the nucleus accumbens was unchanged. The relationship of striatal sigma receptors with decreased peripheral activity suggest that sigma receptors could be associated with the development of tolerance following chronic cocaine administration. This modulation of activity by sigma receptors may result from direct or indirect interactions with striatal dopaminergic systems.

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CHRONIC INTRAVENOUS COCAINE AND HIPPOCAMPAL α_2-ADRENERGIC RECEPTORS: RELATIONSHIP WITH ACTIVITY AND DOSE-RESPONSE

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The role of the noradrenergic system in the development of cocaine-induced behavioral modifications is not well understood. Modulation of hippocampal glutamate efferents to the nucleus accumbens by α_2-adrenergic receptors may have importance in the behavioral modifications observed following chronic cocaine administration. The effect of chronic i.v. cocaine (0.5, 1.0, 3.0 mg/kg) administration for 14 days on α_2-adrenergic receptor density in the hippocamus and locomotor activily following chronic cocaine administration was investigated. Male Sprague-Dawley rats implanted with an intravenous access port (Mactutus, *et. al.,* 1994) were randomly assigned to activity chambers and habituated during two 60 minute test sessions following injection of heparinized saline. Total, peripheral and central activity data were then collected at five minute intervals during the 60 minute alternate daily test sessions. Animals were sacrificed 24 hours after the last injection and the density of α_2-adrenergic receptors was determined as previously described using 2 nM [^{3}H]RX821002 (Wallace, *et. al.,* 1994). Receptor binding and activity data were analyzed using ANOVA and multivariate regression. [^{3}H]RX821002 labeling of hippocampal α_2-adrenergic receptors was negatively related to the dose of cocaine with 0.5 mg/kg exhibiting the greatest decrease (15%) in α_2-adrenergic receptor density. Decreased hippocampal α_2-adrenergic receptor density may indirectly effect dopaminergic transmission in the nucleus accumbens/striatum by decreasing the inhibition of glutamate efferents. These data suggest that α_2-adrenergic receptors are involved in a intricate circuit incorporating noradrenergic and possibly glutamatergic/dopaminergic pathways during the development of cocaine-induced behavioral modifications.

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EFFECTS OF 5-HT DEPLETION ON THE BEHAVIORAL AND ELECTROPHYSIOLOGICAL ACTIONS OF COCAINE

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We have previously demonstrated the involvement of 5-HT_{1A} receptors in the suppression of dorsal raphe (DR) serotonin (5-HT) neurons by cocaine (COC) and also possibly in the development of COC sensitization. The following studies were performed to further explore the role of 5-HT_{1A} receptors and DR 5-HT neurons in the behavioral and electrophysiological effects of COC. Male Sprague-Dawley rats were treated with saline (1 ml/kg) or the neurotoxin *dl*-fenfluramine (FEN; 12 mg/kg s.c., b.i.d., four days) in order to deplete 5-HT from fine fiber projections arising from the DR. Using single unit extracellular recording techniques, no difference in the COC-sensitivity of DR 5-HT cells was observed between saline- and FEN-treated rats 36 hours following treatment in preliminary studies (N=3). However, two weeks after FEN treatment, the ED_{50} for COC inhibition of DR 5-HT cells was shifted 1.8 fold to the left in FEN-treated rats (N=5-8). In contrast to the supersensitivity observed in this electrophysiological assay, unconditioned locomotor activity (LMA) induced by COC (15 mg/kg) was not significantly altered by FEN treatment at either time point. To determine the involvement of 5-HT_{1A} receptors in these divergent results, the 5-HT syndrome induced by 8-OH-DPAT was examined at both time points after FEN treatment (N=8). The intensity of 8-OH-DPAT-induced behaviors was generally reduced at 36 hours, and increased at two weeks, following FEN treatment compared to controls (N=6-10). Thus, 5-HT_{1A} receptors are subsensitive at 36 hours and supersensitive at two weeks following treatment with FEN. This 5-HT_{1A} receptor supersensitivity may explain the supersensitivity of DR 5-HT cells to COC observed two weeks following FEN treatment. The findings that COC-induced LMA was not altered by 5-HT depletion with FEN may indicate mat serotonergic modulation of COC-induced LMA does not involve DR neurons.

EFFECTS OF COCAINE ON THE RESPONSIVENESS SOMATOSENSORY CORTICAL NEURONS TO MYSTACIAL VIBRISSAE STIMULATION

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In humans cocaine has been reported to heighten awareness of the sensory surround and induce sensory hallucinations. Although considerable effort has been put forward to identify the neural basis of cocaine's euphorogenic properties, there have been few studies aimed at investigating the drug's influence on sensory signal processing. Our aim has been to examine the effects of cocaine on somatosensory cortical neuronal responsiveness to peripheral activation of afferent synaptic pathways. Extracellular recordings were obtained from single units in the barre1 field cortex of halothane-anesthetized rats. Cellular responses to mechanical displacement of individual whiskers on the contralateral face were monitored before and after systemic administration of cocaine (0.75 mg/kg i.v.). Control responses to vibrissae stimulation consisted of an initial excitatory burst (E1), a post excitatory suppression of activity (I1) and a secondary excitatory discharge (E2). The effects of cocaine on spontaneous discharge were variable but generally slight increases in firing rate were noted. Following cocaine administration, E1 responses were unchanged or within ± 20 % of control. However, E2 responses were increased from 100-200% above control levels. These acute effects of cocaine were rapid in onset (2 min) and short in duration (20 min) and were consistent with the reported time course of cocaine's biochemical and behavioral actions. To identify the monoamine system involved in the E2 potentiation, we utilized DSP4 (noradrenergic neurotoxin) and PCPA (5HT depletion). We demonstrated that in rats treated with DSP4, cocaine-induced increases in E2 were routinely observed (n=12 cells), but were abolished in the PCPA treated rats (n=10 cells). We have also shown that fluoxetine (5HT reuptake blocker) can reliably mimic cocaine enhancement of E2 responses in somatosensory cortical neurons. These results implicate a 5HT-dependent mechanism in the facilitation of E2 responses and suggests that cocaine can prominently influence neuronal responsiveness to synaptic stimuli in brain circuits that are not usually associated with dopamine or the central reward system.

COCAINE-INDUCED NEUROENDOCRINE AND BEHAVIORAL RESPONSES IN FISCHER AND LEWIS RATS

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Recent data indicate that individual vulnerability to psychostimulant addiction may be related to drug-induced effects on adrenocotical secretion. Thus, strain differences in hypothalamic-pituitary-adrenocortical (HPA) axis activity could be an factor in the variability in the response to the reinforcing effects of drugs of abuse. The present study investigated the neuroendocrine and behavioral responses to cocaine in inbred rat strains, Lewis (LEW) and Fischer (F344), which have been shown to elicit different adrenocortical responses to various stimuli and to orally self-administer cocaine at different rates. We compared the acute effects of cocaine (0-60 mg/kg, ip) on plasma corticosterone (CS) and adrenocorticotropin hormone (ACTH). Dose-related increases in plasma CS and ACTH were observed in both the LEW and F344 rats following cocaine administration. However, LEW rats displayed an enhancement in the magnitude of the CS and ACTH response. We also compared the acute effects of cocaine (0-40 mg/kg, ip) on hypothalamic corticotropin-releasing factor (CRF). Both strains displayed a decrease in CRF, but the response was greater in F344 rats. Cocaine-induced locomotor activity decreased in F344 rats over 60 minutes, while LEW rats displayed a sustained level of activity. LEW and F344 rats were trained to press a lever under a fixed-ratio one schedule (FR1) of food reinforcement and then were tested for acquisition of intravenous cocaine self-administration (0-1.0 mg/kg/infusion). LEW rats intravenously self-administered cocaine at lower doses (0.062 mg/kg/infusion) than F344 rats (0.25 mg/kg/infusion). These data suggest that the strain differences in HPA axis and behavioral responses to cocaine could be related to the variability in intravenous cocaine self-administration observed in LEW and F344 rats.

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DIFFERENTIAL EFFECTS OF COCAINE AND AMPHETAMINE ON LOCOMOTOR ACTIVITY IN SPONTANEOUSLY HYPERTENSIVE AND WISTAR-KYOTO RATS

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Differences in central neurochemical transmission between spontaneously hypertensive (SHR) and normotensive Wistar-Kyoto rats (WKY) have been reported. It has been suggested that brain dopamine systems play a role in the regulation of blood pressure and the development of spontaneous hypertension in rats. The present studies were undertaken to ascertain whether dopamine-mediated behavioral responses were different in SHR and WKY. Male rats were administered amphetamine or cocaine, ip and data collected with automated activity monitor. The basal levels of locomotor activity and stereotyped behavior were similar in SHR and WKY. Amphetamine-induced behavioral responses were lower in SHR than in WKY ($p < 0.05$ at 0.3 and 0.6 mg/kg). No significant differences were found between the responses of SHR and WKY to cocaine. Nimodipine had no effect on amphetamine-stimulated activity in the two strains of rats. In contrast, cocaine-stimualted activity in WKY rats (but not in SHR) was dose-dependently decreased by nimodipine. Compensatory mechanisms may play a role in the response of the SHR to amphetamine and cocaine.

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ENHANCEMENT OF THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE BY L-NAME IS BLOCKED BY D_1 AND D_2 ANTAGONISTS

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The nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME) has an indirect influence on dopamine (DA) neurotransmission. In rats trained to discriminate 10 mg/kg cocaine from vehicle, pretreatment with 100 mg/kg L-NAME produced leftward shifts in the dose-response curves for cocaine, (+)-amphetamine and GBR 12909, with 3-fold or greater decreases in the ED_{50} (Kantak and Edwards, 1994). In order to evaluate the potential role of DA in mediating the effects of L-NAME under these experimental conditions, antagonism studies with DA receptor blockers were conducted. As in past experiments, L-NAME produced a 3-fold decreaze in the ED_{50} for cocaine. Pretreatment with 0.03 and 0.06 mg/kg haloperidol produced dose-dependent increases in the ED_{50} for cocaine, with the degree of rightward shift greater following the L-NAME treatment condition (2.1- and 3.8-fold, respectively) than following the saline treatment condition (1.4- and 2.9-fold, respectively). Pretreatment with SCH 23390 also produced dose-dependent increases in the ED_{50} for cocaine, with the degree of rightward shift produced by 0.003 and 0.01 mg/kg SCH 23390 greater following the L-NAME treatment condition (1.9- and 2.8-fold, respectively) than following the saline treatment condition (1.1- and 1.4-fold, respectively). These findings suggest that D_1 and D_2 receptor mechanisms are important for mediating the DS effects of cocaine and that both D_1 and D_2 receptor mechanisms may play an important role for mediating the enhancing influence of L-NAME on the DS effects of cocaine.

DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE IN MALE AND FEMALE RATS

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Gender differences in rates of drug addiction may reflect biological differences in sensitivity to the subjective or reinforcing properties of abused substances. The present study was conducted to determine whether female and male rats show any differences in rate of acquisition of a cocaine discrimination, and whether there are sex diffeferences in sensitivity to the subjective effects of substituted agonists. Six female and six male Sprague-Dawley rats were trained to discriminate 5.6 mg/kg i.p. cocaine hydrochloride from saline in a two-lever, food-reinforced operant procedure. Female and male rats acquired the cocaine discrimination at the same rate (mean ± SEM, 47.9 ± 7.2 vs. 43.4 ± 8.4 sessions respectively). Further, the ED_{50} of cocaine for female rats (2.14 ± 0.39 mg/kg) was not significantly different from that for males rats (2.55 ± 0.61 mg/kg). d-Amphetamine (0.1-.56 mg/kg) substituted for cocaine in a dose-dependent manner. In contrast, neither the mu opioid agonist morphine (0.3-5.6 mg/kg), the kappa opioid agonist U69,593 (0.03-0.18 mg/kg), nor the delta opioid agonist BW373U86 (0.3-3.0 mg/kg) substituted for cocaine. Discriminative stimulus effects of cocaine also were compared to cocaine's locomotor effects in female and male rats. This study suggests that there are no significant sex differences in the discriminative stimulus properties of cocaine during acquisition or maintenance in the rat.

ACKNOWLEDGEMENTS:

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ATTENUATION OF COCAINE HYPERAROUSAL IN RHESUS MONKEYS WITH (+)-N-3(*p* FLUOROBENZOYL)PROPYL-3 β METHYL-4β-PHENYL-4α-PROPIONYLOXYPIPERIDINE ((+)-I-184))

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We previously reported (Aceto, *et. al.,* The FASEB J. 4 1990) that one of a series of α-prodine-like compounds with a unique combination of mu-opioid-agonist and dopaminergic- (D_2) antagonist properties, dose- dependently attenuated signs associated with cocaine (COC) hyperarousal (rausch) in rhesus monkeys. We have now extended these studies to include both the racemate and the (+)-isomer of one in the series of β-prodine-like compounds (I-184). Groups of three or four rhesus monkeys were randomly selected to receive s.c. either vehicle or (+)-I-184 (0.003 or 0.012 mg/kg) 0.5 hours before the i.v. administration of COC (1.0 mg/kg) or saline vehicle. Hyperarousal signs (such as restlessness, checking, feinting, escape attempts, tremors, searching etc.) were scored during three minute periods for a total of 15 minutes. While pretreatment with the higher dose of (+)-I-184 produced attenuation of signs to control levels, the lower dose was without effect. Studies with the racemate of I-184 (0.006, 0.025 and 0.1 mg/kg) produced similar results. However, convulsions or death occurred in animals receiving any dose of the racemate whereas no such toxic effects were noted with the (+)-isomer. Finally, toxicity may be attributable to the (-)-isomer.

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PLASMA BUTYRYLCHOLINESTERASE ACTIVITY IN MONKEYS: A CROSS-SPECIES COMPARISON

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Plasma butyrylcholinesterase (BChE) is the major cocaine-metabolizing enzyme in both human and nonhuman primates. Preliminary studies in rodents and retrospective studies in cocaine users seeking medical treatment suggest an inverse relationship between BChE activity and the response to cocaine (Gorelick, *et. al.,* 1993). No relevant data exist for non-human primates. The objective of the current study was to determine plasma BChE levels in two species of non-human primates. We evaluated activity levels in 16 individual monkeys (12 male rhesus monkeys and four male squirrel monkeys). There were significant cross-species (rhesus vs squirrel monkeys) differences in BChE activity ($t(12)= 7.9$, $p<.001$), with rhesus monkey (4.98 ± 0.24 units/L) showing much higher levels of activity than squirrel monkeys (1.70 ± 0.24). Age differences and previous drug history do not appear to account for those differences. Therefore, we would expect to see differences in cocaine metabolism across these two species, with rhesus monkeys more closely resembling human subjects.

PHARMACOPHORE MAPPING: SYNTHESIS OF LIGANDS SELECTIVE FOR THE α5β2γ2 BzR SITE

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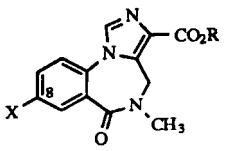
The BzR site is believed to be formed, at least in part, by the α--subunit of the GABAA receptor since compounds exhibit different affinities depending on the type of α-subunit present. In order to investigate the structural requirements for selectivity at BzR sites, a series of 8-substituted imidazobenzodiazepine-6-ones were synthesized and tested for their ability to displace [^{3}H] Ro15-1788 from cells expressing human $GABA_A$ receptors of structure α1β2γ2, α2β2γ2, α3β2γ2, α5β2γ2 and α6β2γ2. It appears position-8 is an important determinant of α-selectivity. In fact ligands 2, 3, and 4, as well as **5** and **6** are the most α-**5** selective ligands reported to date. In contrast, 3EBC (like zolpidem) binds to α1β2γ2 sites but not to the α5β2γ2 subsite. In regard to pharmacophore mapping, ligands prepared in this series will be compared via molecular modeling to those selective for α1β2γ2 sites as well as to those which bind to α6β2γ2 (DI) sites.



X	R	α1β3γ2	α2β3γ2	α3β3γ2	α5β3γ2	α6β3γ2
N_3(**1**)	ethyl	3.3	2.6	2.5	0.26	3.8
C≡CH (2)	ethyl	28.4	21.4	25.8	0.49	28.8
C≡CSiMe$_3$ (**3**)	ethyl	121.1	141.9	198.4	5.00	113.7
C≡CH (**4**)	*t*-butyl	26.9	26.3	18.7	0.40	5.1
C≡CSiMe$_3$ (**5**)	*t*-butyl	197.0	142.6	255.0	2.61	58.6
	no ester					
Cl (**6**)	CH_2OMe	>300	>300	>300	38.1	>300
3EBC	β–carboline	6.4	25.1	28.2	826	>1000

MIDAZOLAM SELF-INJECTION IN BABOONS

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A significant proportion of patients prescribed benzodiazepines (BZD) develop patterns of chronic daily use and concurrent physical dependence. In preclinical studies, however, the demonstration of BZD reinforcement has been equivocal. The present ongoing experiments sought to establish reliable chronic BZD self-injection in baboons. Self-injection of midazolam (MDZ, 0.004-1.0 mg/kg) was examined in baboons (n=4) under conditions of continuous drug availability. Baboons with intravenous catheters self-injected MDZ or saline under a fixed-ratio schedule (FR30). Reliable self-injection of MDZ was maintained at doses of 1.0, 0.25 and 0.0625 mg/kg/injection, but was not maintained during saline and 0.004 mg/kg/inj. MDZ injections were distributed over the 24 hour session, although fewer injections were taken during the low light cycle. At low MDZ doses (0.0156-0.0625) baboons took multiple injections with very short inter-injection intervals. Flumazenil pretreatment (0.1 mg/kg, i.v.) after at least 20 days of chronic 0.25 mg/kg/injection MDZ produced distinct behavioral signs of physical dependence such as tremors, jerks, bruxism and reduced food intake. When MDZ was discontinued after at least 20 days of self-injection of 0.25 mg/kg/injection, similar behavioral signs of physical dependence were evident in some baboons within 24 hours, and in all four baboons by the third day. These data indicate that MDZ serves as a reinforcer in a dose-dependent manner and provides reliable self-injection baselines to further examine the relationship between physical dependence and reinforcing effects of BZD.

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STUDIES OF ORAL REINFORCEMENT BY BENZODIAZEPINES IN RHESUS MONKEYS

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Previous research has shown that midazolam functions as a reinforcer for rhesus monkeys when delivered orally and that diazepam maintains self-administration when substituted for midazolam (JPET 271:200, 1994). This report describes progress in three ongoing studies of benzodiazepine reinforcement. In the first study, diazepam has been established as a reinforcer in three monkeys using an ethanol fading procedure (*i.e.,* not substitution). Concentration manipulations show orderly inverted U-shaped dose-response curves for diazepam reinforced behavior. In the second study, a high dose vs. low dose choice procedure has been used in two monkeys to show that higher concentrations of both diazepam and midazolam consistently are preferred to lower concentrations. These findings support the hypothesis that higher concentrations are more reinforcing than lower concentrations. In the third study, both triazolam and alprazolam have maintained self-administration behavior when substituted for midazolam in two monkeys. These studies clearly demonstrate that benzodiazepines are reinforcers when delivered orally.

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COMPARING THE REINFORCING EFFICACY OF ORALLY SELF-ADMINISTERED TRIAZOLAM AND ALPRAZOLAM IN BABOONS

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This study compared oral self-administration (OSA) of a low triazolam (TRZ; Halcion) concentration with OSA of alprazolam (APZ; Xanax). Prior OSA work with TRZ showed that the opportunity to ingest this drug did not provide strong evidence for TRZ reinforcement (Ator and Griftiths, *Psychopharmacology,* 1992, 108:301-312). In that study, response requirements were imposed and manipulated at a single high TRZ concentration (0.32 mg/ml or higher). More recently, although APZ and a low TRZ concentration (0.08 mg/ml), respectively, were consumed in higher volumes than vehicle when each was available separately, a preference test, in which drug (APZ or TRZ) and vehicle were concurrently available, did not strongly indicate drug reinforcement. In contrast, under a fixed ratio schedule of drug or vehicle reinforcement, the opportunity to ingest APZ (0.01 - 0.16 mg/ml) or TRZ (0.08 mg/ml) maintained higher response requirements for access to drug than for access to vehicle in three baboons, even when the response requirements for each drink were rather high. Lower APZ concentrations actually maintained higher response requirements than did higher concentrations. These results with a relatively lower TRZ concentration, in conjunction with the APZ data, indicate that responding maintained by orally delivered benzodiazepines may be more resistant to increases in response requirements at lower than at higher concentrations and may be a function of the fact that more fluid must be ingested at low concentrations to obtain a threshold total dose during the period of drug access.

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PHYSICAL DEPENDENCE AFTER LOW OR HIGH DIAZEPAM (DZP) DOSES IN BABOONS

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Physical dependence on DZP was assessed in male baboons after administration of once daily 0.5 mg/kg, p.o. DZP (n=4) or continuous 20 mg/kg/day, i.g. DZP (n=3). Responding was maintained under a fixed ratio 30 schedule of food pellet delivery. Food pellets were available 22 hours/day. Behavior was scored during one hour observational sessions using rating scales. A variety of behaviors, postures and movements, level of coordination, activity and sedation and tremor were scored. In baboons receiving 0.5 mg/kg/day DZP, the benzodiazepine antagonist flumazenil (5.0 mg/kg, i.m.) precipitated a withdrawal syndrome (including decreases in food intake, retching and vomiting) after only two weeks, and was seen throughout the ten months of DZP administration. During spontaneous withdrawal when vehicle was substituted for 0.5 mg/kg DZP, there were decreases in food intake seen within one to three weeks of DZP termination in two of four baboons, but no other withdrawal signs. In contrast, when vehicle was substituted for 20 mg/kg DZP, withdrawal signs (including limb and body tremor) and severe disruptions in food intake appeared within one to two weeks after termination of DZP in all baboons. In two of the three baboons, the disruptions in food intake was still apparent six to seven weeks after termination of chronic DZP. Thus, physical dependence developed after chronic 0.5 mg/kg DZP, however, it was less severe than after chronic high (20 mg/kg) DZP doses.

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TOLERANCE AND CROSS-TOLERANCE BETWEEN DIAZEPAM AND PENTOBARBITAL IN A DRUG-DISCRIMINATION PROCEDURE

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Diazepam (DZP) and pentobarbital (PB) are allosteric modulators of the GABAA receptor complex such that they both enhance the chloride (Cl-) conductance mediated by GABA. In order to further characterize the interactions of these modulators on this neurotransmitter system, the present experiment tested the hypotheses that: 1) chronic administration of PB would confer tolerance to PB and cross-tolerance to DZP and, 2) chronic administration of DZP would confer tolerance to DZP and cross-tolerance to PB. Thirty rats were trained to detect PB (10.0 mg/kg) from saline; an additional 30 rats were trained to detect DZP (5.6 mg/kg) from vehicle. These discriminations were trained using a two-lever choice procedure where food was available under a fixed-ratio 10 (FR10) schedule of reinforcement. Both PB (1.0 - 17.8 mg/kg) and DZP (1.0 - 17.8 mg/kg) fully substituted for one another. Following substitution testing, the effects of chronic PB (32 mg/kg/8 hours for seven days) or DZP (20.0 mg/kg/8 hours for seven days) administration on these dose-effect curves were determined. In both discriminations, the chronic administration of PB produced a significant shift to the right of the PB dose-effect curve without significantly shifting the DZP dose-effect curve. In both discriminations, the chronic administration of DZP produced a significant shift to the right of the DZP dose-effect curve without significantly shifting the PB dose-effect curve. The present results suggest that tolerance to PB is not sufficient to produce cross-tolerance to DZP; similarly, tolerance to DZP is not sufficient to produce cross-tolerance to PB. Taken together, these results suggest that the mechanisms mediating tolerance to the discriminative stimulus properties of DZP and PB are functionally dissociated.

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ETHANOL SUBSTITUTES FOR A MIXTURE OF DIAZEPAM AND KETAMINE IN A DRUG DISCRIMINATION PARADIGM IN RATS

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In drug discrimination experiments, when EtOH is used as a training stimulus, benzodiazepines (such as diazepam, DZP) as well as noncompetitive NMDA antagonists (such as ketamine, KET) substitute for EtOH; in contrast, when a benzodiazepine or an NMDA antagonist is used as a training stimulus EtOH does not reliably substitute. In the present experiments, we trained rats to discriminate a mixture of DZP and KET and tested the hypothesis that EtOH would substitute for this drug combination. Using a two-lever choice procedure with food as a reinforcer 16 rats were trained to discriminate a mixture of DZP (5.6 mg/kg) and KET (10 mg/kg) from vehicle. The DZP-KET mixture substituted for itself in a dose-dependent manner. When administered separately, both DZP and KET substituted for the mixture with full substitution occurring at 5.6 and 17.8 mg/kg, respectively. Furthermore, EtOH also substituted fully for the mixture at 1 g/kg. There was no cross-substitution between DZP and KET in rats trained to discriminate DZP (5.6 mg/kg, n = 12) or KET (10 mg/kg, n = 6) individually from vehicle. In addition, EtOH did not substitute for the training drug in either of these discriminations. These results suggest that simultaneous action of GABA agonist and NMDA antagonist mechanisms is necessary to produce EtOH-specific discriminative stimulus.

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TOLERANCE TO THE DISCRIMINATIVE AND REINFORCING STIMULUS EFFECTS OF KETAMINE DEVELOPS DURING TRAINING

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This study determined whether tolerance developed to the discriminative and/or reinforcing stimulus effects of ketamine. Nineteen male Long Evans rats were trained to discriminate ketamine (10 mg/kg) from saline. After discriminative control by ketamine was established, chronic ketamine (32 mg/kg i.p.) was given every eight hours for seven days. No shift in the dose-response curve was found following this treatment. The failure of chronic ketamine to shift the dose-response curve would generally suggest that no tolerance develops to the discriminative stimulus effects of ketamine. However, after a two week period in which animals received no drug, a three-fold shift to the left in the dose-response curve was observed. Thus, based on the leftward shift in the dose-response curve observed following the two week rest, it may be possible that maximal tolerance had developed during daily training. Comparable results were found in a self-administration paradigm. Eleven male F-344 rats were trained to self-administer ketamine i.v. (16 mg/kg) under an FR2 schedule of reinforcement. After stable baselines were established and dose-response curves determined, tats were rested for two weeks. Dose-response curves obtained after this two week period showed a three-fold shift to the left. Rats were then given chronic ketamine (32 mg/kg i.p.) every eight hours for seven days. The dose-response curve obtained following chronic ketamine did not differ from the baseline curve. The self-administration results support the proposal that maximal tolerance to ketamine develops during daily training, and explains the failure of chronic treatment with the drug to shift the dose-response curve in the discrimination procedure.

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ROLE OF OPIOID SYSTEM IN THE DIAZEPAM-INDUCED ANTICONFLICT ACTION IN MICE

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To investigate the role of opioid system in the diazepam-induced anticonflict action, first, the effects of μ-, δ- and κ-opioid receptor antagonist on diazepam-induced anticonflict action were examined in mice using Vogel type conflict paradigm. Mice were injected i.p. with diazepam at 30 minutes before test session. Diazepam (1 mg/kg) significantly produced anticonflict action without affecting spontaneous drinking behavior. The diazepam-induced anticonflict action was abolished by pretreatment with β-funaltrexamine and nor-binaltorphimine, but not with naltrindole. These findings suggest that endogenous opioid system which is mediated by μ- and κ-opioid receptor may be partially related to the anticonflict action of diazepam. Furthermore, the anticonflict action of μ-opioid receptor agonist morphine and κ-opioid receptor agonist U50,488H were examined. Mice were injected s.c. with morphine or U50,488H at 30 minutes before test session. U50.488H (1.0 mg/kg), but not morphine, significantly produced an anticonflict action. In addition, the U50.488H did not affect the spontaneous drinking behavior. Furthermore, the U50,488H-induced anticonflict action was antagonized by pretreatment with nor-binaltorphimine. Therefore, it is suggested that antianxiety action may be produced by the activation of κ-opioid receptors.

PREDICTORS OF HYPNOTIC SELF-ADMINISTRATION

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Insomniacs self administer pills (placebo and triazolam) at bedtime at high and persistent rates compared to daytime studies. This study determined whether or not the severity of insomnia (documented with sleep recordings) is predictive of hypnotic self administration. Sixty-four subjects, 25 women and 39 men, aged 35.2±5.8 years, (56 with insomnia and eight healthy normals) have been evaluated. All were in good health (except for the insomnia) with no medical or psychiatric diseases and no history of alcoholism or drug abuse. On four to six sampling nights, 30 minutes before bedtime, subjects received color-coded placebo or triazolam 0.25 mg which was followed by four to seven choice nights on which they could choose to self administer the same color-coded pill of the sampling nights. The percentage of placebo and drug choices did not differ, but patients and normals did differ (81% vs 26%). In a multiple regression analysis (maximum R selection) no single one, or group of, MMPI scales were predictive of percentage of pill choices. In constrast, the extent of sleep disturbance predicted (R=.54) the likelihood of self administering a pill before sleep, regardless of whether the pill was placebo or active drug. These findings suggest that insomniacs' high and persistent self administration of pills is insomnia-relief-seeking behavior and not drug abuse.

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METHADONE-BUPRENORPHINE TRANSFER IN BRITISH OPIATE ADDICTS

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This is the first completed study of buprenorphine (BUP) in opiate addicts in the UK. Thirteen opiate addicts who met DSM-III-R criteria for opiate dependence and were stabilised on 20-30 mg/day oral methadone (M) were transferred for three days to BUP 4 mg/day sublingually as outpatients. Saccadic eye movements (SEM) were used to quantify central opiate effects. SEM have potential advantages over pupillometry as they are sensitive, reliable, can be repeated frequently and have minimal conscious input once initiated. Self report measures included the ARCI short form (MGB, PCAG, and LSD scales), the agonist-antagonist adjective checklist (agonist and withdrawal scales) and visual analog scales (VAS). Subjects recieved £45 ($70) in vouchers for taking part.

A) Positive effects of BUP: VAS "good effects" became elevated ($p=0.05$) and the "drug high" score remained low over the three days. There were no significant changes in the agonist scale, the MGB scale and the observer rated withdrawal scale. Subjects reported a 77% likelihood of accepting BUP in place of M for maintenance therapy. **B) Negative effects of BUP:** Withdrawal symptoms increased ($p=0.006$) pre-BUP on day 2 but were clinically mild. On day 3 the withdrawal score had returned to near baseline. A similar pattern was observed with the LSD and PCAG scale. However on day 3, "Bad effects" ($p=0.03$) and heart rate ($p=0.02$) remained elevated and systolic BP reduced ($p<0.005$). **C) SEM:** SEM peak velocity decreased non-significantly to the peak effect of the BUP (3 hours), and then increased significantly pre-BUP on day 2 ($p=0.02$) at the time of the maximal withdrawal effects. Pupillography revealed uo significant differences. These findings illustrate the acceptability of BUP to British opiate addicts, and the potential of SEM as a measure of central opiate effects.

ALPRAZOLAM SELF-MEDICATION IN ANXIOUS PATIENTS: DEMONSTRATION OF REINFORCING EFFECTS

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Fourteen outpatients with generalized anxiety or panic disorder were given alprazolam (0.5 mg) and placebo capsules, under double-blind conditions, for self-medication "as needed" (p.r.n.). On each weekly clinic visit, patients took home 56 medication capsules contained in electronic bottles which recorded the date and time of each capsule use. Alprazolam or placebo were provided in color-coded capsules. Patients received one medication/capsule-color on week one and the alternative on week two. During the next four weeks (weeks #3-6) they received both colors to determine preference. Measures of drug use included the times and amount of drug and placebo consumption and the preference for alprazolam. Other measures included subjective ratings of drug effect, anxiety, and personality variables. During the first two weeks, patients consumed alprazolam and placebo in similar patterns suggesting a non-specific bias towards medication use. However, during the choice phase (weeks #3-6), 11 of 14 patients preferred (> 90%) alprazolam over placebo. The numbers of capsules ingested per day varied but were within normal prescription limits. Compared to placebo, alprazolam produced sedative side effects, but patients still rated it as helpful. However, anxiety measures did not detect an anxiolytic effect of alprazolam. Several demographic and psychological variables predictively correlated with measures of drug use behavior. In conclusion, alprazolam was shown to be a reinforcer for anxious patients self-medicating for anxiety.

DISCRIMINATIVE STIMULUS EFFECTS OF TRIAZOLAM, ZOLPIDEM, OXAZEPAM, AND CAFFEINE IN HUMANS

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The discriminative stimulus effects of triazolam (TRZ), zolpidem (ZLP), oxazepam (OXP) and caffeine (CAF) were assessed in seven healthy, paid volunteers trained to discriminate placebo and TRZ (0.25 mg/70 kg). The study was conducted in three phases. During the training phase, placebo and TRZ (0.25 mg), identified by letter codes (*e.g.,* Drug A or B), were each administered two times in mixed order across sessions and subjects were instructed to attend to the drug effects because in subsequent sessions they could earn money by correctly identifying which drug they had received. In a test-of-acquisition phase, the drugs were not identified and subjects reported their drug identification four hours after drug administration. Five of seven subjects acquired the discrimination (*i.e.,* 280% accuracy). These five subjects then completed a dose-response testing phase in which 0, 0.0625, 0.125, 0.25 and 0.5 mg/70 kg TRZ were tested four times each, and subjects were paid for correct or incorrect discriminations during test sessions. These test doses of TRZ increased TRZ-appropriate responding as a graded function of dose. Finally, four of the five subjects participated in a novel-drug-test phase in which ZLP (0, 2.5, 5, 10 and 20 mg/70 kg), OXP (0, 3.125, 6.25, 12.5 and 25 mg/70 kg) and CAF (0, 50, 100, 200 and 400 mg/70 kg) were tested. Each test dose was generally administered two times. ZLP and OXP dose-dependently increased TRZ-appropriate responding. In general, CAF did not substitute for TRZ. These data suggest a TRZ (0.25 mg/70 kg)-placebo discrimination can be acquired, and is pharmacologically specific. These results also suggest that the discriminative stimulus effects of ZLP are similar to those of TRZ despite its somewhat unique benzoeiazepine receptor-binding profile.

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TRIAZOLAM PHYSICAL DEPENDENCE ASSESSED ACROSS INCREASING DOSES UNDER A ONCE-DAILY DOSING REGIMEN

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Physical dependence to the quickly-eliminated, potent hypnotic triazolam (TRZ) occurred in the context of an oral self-administration study (Ator and Griffiths, *Psychopharmacology,* 1992, 108:301-312). Daily access was only two to three hours but the self-administered doses were high. We now have investigated behavioral and physical-dependence-producing effects of low, once daily, doses in baboons using a cumulative-dosing procedure. A low but discriminable TRZ dose (0.032 mg/kg, p.o.) was determined in four baboons that had been trained to discriminate lorazepam in a drug discrimination study. Three other baboons then were studied under a procedure in which they were dosed i.g. once daily. The successive 17-day conditions were: Vehicle, 0.032, 0.1, 0.32, and 1.0 mg/kg per day. Then 1.0 mg/kg/day was given for about four weeks as a slow, continuous i.g. drip. Food intake was dose-dependently increased as were signs of ataxia and time to complete a fine motor task. A mild to strong flumazenil-precipitated withdrawal syndrome was observed when tested on day 14 of each TRZ dose condition. Thus, despite its short half-life (TRZ blood levels were virtually zero 24 hours after each bolus dose), once-daily administration was sufficient to produce physical dependence to TRZ. Discontinuing TRZ reduced food intake, which remained low for four weeks or more. Overt signs of withdrawal, including tremor but not seizures, were seen in the first two weeks.

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INTERACTIONS BETWEEN CIRCULATING OVARIAN HORMONES AND RESPONSE TO TRIAZOLAM IN WOMEN

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Recent *in vitro* studies suggest that certain metabolites of ovarian hormones, such as allopregnanolone, act on the GABAA receptor complex. It is not known whether variations in levels of these metabolites related to the menstrual cycle affect mood or behavior. This study was designed to investigate the interaction between circulating ovarian hormones and acute response to triazolam in women with normal menstrual cycles. Healthy women (N=12) participated in six laboratory sessions over a two-month period, in a within-subject, double-blind, placebo-controlled study. Each subject received a single oral dose of triazolam (0.25 mg) and placebo at each of three phases of the menstrual cycle (follicular, ovulatory, luteal). The day of ovulation was identified by the surge in 6 p.m. urinary LH levels. Subjective, psychomotor and physiological responses were measured for 12 hours after drug administration, and plasma samples were obtained to determine levels of triazolam, progesterone and estrogen. Triazolam produced its expected sedative effects at all three phases of the cycle, but the magnitude and quality of the drug's effects did not vary across the three cycle phases. Clearance of triazolam was slower in the luteal compared to the follicuhar phase, but Cmax and Tmax were similar across phases. These findings suggest that hormonal fluctuations during the menstrual cycle do not systematically influence acute response to benzodiazepines.

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HUMAN TRIAZOLAM DISCRIMINATION WITH A NOVEL-RESPONSE OPTION: EFFECTS OF MEPROBAMATE

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A novel-response procedure that provides a response alternative appropriate for novel-drug effects increases the selectivity of human triadam (TRZ) discrimination. Humans (N=6) were trained to discriminate TRZ (0.32 mg/70 kg, p.o.) from placebo. Dose-effect curves were then determined for TRZ (0.03-0.32 mg/70 kg) and meprobamate (MEP; 100-1000 mg/70 kg) under a two-response procedure and/or the novel-response procedure. Four subjects were tested under both procedures in a crossover design and an additional two subjects were tested only under the novel-response procedure. Under both procedures, TRZ occasioned 100% TRZ-appropriate responding in all subjects tested. Under the two-response procedure, MEP completely substituted for TRZ in three of four subjects. Under the novel-response procedure, MEP occasioned 100% TRZ-appropriate responding (n=2), 100% novel-appropriate responding (n=2) and either 100% TRZ- or 100% novel-appropriate responding, depending on the dose (n=2). This pattern of responding on both the novel- and drug-alternative suggests that MEP's stimulus effects overlap, but are not the same as TRZ's. Self-reported effects did not differentiate MEP from TRZ and did not vary systematically across the two discrimination procedures. Considering the current results with MEP in the context of results with other drugs tested under the novel-response procedure suggests that the amount of triazolam-appropriate responding remaining when the novel-appropriate alternative is present may provide the finest resolution for making distinctions between drugs with similar discriminative stimulus effects. Rank ordering drugs according to the amount of TRZ-appropriate responding *in the presence of the novel-response alternative* results in the following relative similarity to TRZ: TRZ = diazepam > lorazepam > secobarbital = MEP > buspirone > hydromorphone > amphetamine = caffeine. Thus, the novel-response procedure permits finer distinctions amongst sedative/hypnotics than are possible using standard two-response drug discrimination procedures.

DISSOCIATION OF SELF-REPORTS AND DISCRIMINATIVE PERFORMANCE

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Dissociation between self-reports and responding in the chug discrimination procedure (*i.e.* discriminative performance) occurred under a procedure examining cumulative dosing in human drug discrimination. In this procedure, subjects (n=6) received 0.32 mg/70 kg of triazolam and three placebos across four components in random order (*e.g.,* Placebo-Triazolam-Placebo-Placebo). Typically, dissociation occurred when placebo administered after triazolam was discriminated as placebo, but the self-report score remained triazolam-like. Across subjects, dissociation occurred for at least one out of eight self-reports analyzed on 29 of 39 occasions. Differences were noted between subjects in the degree of dissociation observed. The mean percent dissociation between each self-report and discriminative performance revealed that some measures (*e.g.,* visual analog rating of good drug effects) dissociated more from discriminative performance than others (*e.g.,* visual analog rating the similarity to triazolam). Subjects also accurately discriminated placebo doses administered after triazolam as placebo on 33 of 39 occasions, demonstrating a pattern of within-session responding not previously reported in humans. These results suggest that the concordance between self-reports and discriminative performance typically reported in the literature may be due to methods employed in human drug discrimination studies and not necessarily to a causal relationship between subjective effects and discriminative performance.

DISCRIMINATIVE STIMULUS EFFECTS OF DIAZEPAM AND BUSPIRONE IN A THREE-CHOICE RESPONSE PARADIGM

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A three-choice response paradigm was used to characterize the discriminative and self-reported effects of orally administered diazepam (DZP) and buspirone (BUS) in human subjects with no reported substance abuse or psychiatric histories. Subjects were trained to discriminate DZP (10 mg), BUS (15 mg) and placebo. Drug code identifications were made two hour post drug administration. Subjects were exposed to each drug condition in randomized blocks of sessions until five correct identifications of the last six exposures in each drug condition were made. Drug generalization was then examined with lower doses of DZP (2.5 and 5.0 mg) and BUS (3.75 and 7.5 mg) and placebo. During generalization testing, discrimination accuracy was maintained by interspersed placebo, DZP (10 mg) and BUS (15 mg) training sessions. The three-way discrimination was acquired within a range of in 18-56 sessions (M=25 ± 4 SEM). Lower doses of both DZP and BUS were identified as placebo. Between-subject statistical analyses of responses from "correct guess" training sessions revealed that, relative to placebo, DZP and BUS significantly increased ARCI and VAS scores of sedation and VAS scores of drug strength. Scores of euphoria (MBG), vigor, alertness and motivation were significantly decreased. The subjective effects of DZP and BUS were differentiated by within-subject statistical analyses. Significant between-drug differences were found on at least one scale of either the ARCI, PGMS or VAS across subjects. Unstructured self reports also revealed between-drug differences; anecdotal descriptors reported for BUS, but not DZP, included feelings of nausea, dizziness, prickly or tingly body sensations, anxiousness and agitation.

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VARIABILITY IN HERITABILITY ESTIMATES WITH DIFFERENT MEASURES OF ALCOHOL

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Twin and adoption studies generally have reported evidence for genetic influences in alcoholism. But considerable differences in the amount of variation attributed to genetic and environmental factors exist, which may be due to differences in samples and/or measurement instruments used. This study examined estimates of genetic influences in alcoholism obtained with different measures in the same sample. Therefore, any difference must be attributable to differences in the various instruments used to detect genetic influences. Subjects were 92 mono- and 88 dizygotic twin pairs with information on all measures (Pickens, *et. al.,* 1991). Correlations between the various measures in probands indicated that the measures did only partly measure the same construct. Estimated contributions of additive genetic effects were: 28% heavy use; 24% problems with use ever; 35% quantity; 29% frequency; 31% density (quantity*frequency) of alcohol consumption; 28% Feighner definite alcoholism; 8% Cloninger type 1; 22% Cloninger type II; 49% DSM-III alcohol dependence and 29% DSM-III alcohol abuse/dependence. DSM-III alcohol dependence thus appears to be the most sensitive instrument to detect genetic influences in alcoholism.

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DISPOSITION OF CODEINE IN MALE VS. FEMALE HUMAN HAIR AFTER MULTIPLE DOSES

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Studies of the disposition of codeine into the hair of male (n=7) and female (n=7) subjects after a multiple dose protocol were performed. Caucasian male and female subjects with dark brown to black hair were administered a total dose of 450 mg of codeine over five days (30 mg 3 times a day for 5 days). Analysis of plasma, urine and hair were performed by positive ion chemical ionization GC/MS on a Finnigan Magnum^{TM} mass spectrometer. Hair was plucked from the scalp for five weeks and subsequently cut from the scalp for up to ten weeks. Prior to analysis, plucked hair specimens were cut into two segments: a) proximal 1 cm containing the root, and b) a distal segment containing all remaining hair. In female subjects, the highest mean hair concentration of unconjugated codeine in proximal hair segments was 2.7 ng/mg (± 0.55) at 12 hours after the last codeine dose, with .44 ng/mg (±.20) still remaining at five weeks. Codeine was detected in distal hair segments at one week, with an average mean distal codeine concentration of .54 ng/mg (± .05) for ten weeks. In male subjects, the highest mean hair concentration of unconjugated codeine in proximal hair segments was 2.6 ng/mg ±.34) at 12 hours after the last codeine dose, with no codeine detectable at five weeks. Codeine was not detected in these distal hair segments until two weeks, with an average mean codeine concentration of .08 ng/mg (±.01) for ten weeks. Differences noted in distal codeine hair concentrations between male and female subjects were not explained by plasma pharmacokinetics.

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HAIR PIGMENTATION AS AN IMPORTANT FACTOR IN DRUG INCORPORATION INTO HAIR

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Compounds circulating in the blood-stream may unltimately become incorporated into a growing hair shaft. However, the factors governing this incorporation are poorly understood. Because the ability of melanin to bind many drugs is impressive, we studied the effect of hair pigmentation on the incorporation of drugs and their metabolites in Sprague-Dawley (SD; non pigmented), Dark Agouti (DA; pigmented) and hooded Long-Evans (LE; pigmented and non pigmented) rats. Codeine was administered at 40 mg/kg/day, i.p., for five days. Fourteen days later, hair was collected and analyzed for codeine, morphine and norcodeine by positive-ion chemical ionization GC/MS. The plasma pharmacokinetics for codeine and morphine in DA and SD rats were also obtained. Codeine concentration in the hair of DA rats was six times greater than the concentration in SD rats (0.98 ± 0.10 vs 6.02 ± 1.23 ng/mg hair, respectively). When the plasma AUC values and metabolism differences are considered the DA rats still incorporated about three times more codeine than the SD rats. In the LE rat, a rat which produces both black and white hair, the concentration of codeine in the pigmented hair was 44 times the concentration in non pigmented hair from the same animals (108.1 ± 9.85 vs 2.45 ± 0.27 ng/mg hair, respectively). Similarly large differences were seen for morphine and norcodeine concentrations in hair. It is concluded that pigmented hair possesses a greater capacity to incorporate codeine and its metabolites than does non pigmented hair.

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HUMAN HAIR TRANSPLANTED TO ATHYMIC MICE AS A MODEL OF DRUG INCORPORATION

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In this study, codeine incorporation into human hair transplanted onto athymic mice was evaluated. Human fetal scalp skin was sutured into a subcutaneous pocket created on the lateral thoracic cage of athymic mice. After 60 days, the skin overlying the graft was removed and hair was allowed to grow from viable grafts. Mice then received codeine 20 mg/kg i.p. daily for five days. Hair was cut at the skin surface prior to drug administration (day 0), 28 days after drug administration (day 28), and 56 days after drug administration (day 56). Codeine and morphine were measured in the hair specimens by positive-ion chemical ionization GC/MS using deuterated internal standards. The results are shown on the following table:

Animal No.	Codeine Concentration (ng/mg hair))		
	Day 0	Day 28	Day 56
1	0	7.2	0
2	0	0.5	0
3	0	2.3	0
4	0	2.7	0
5	0	1.5	0

These data demonstrate that codeine, but not its metabolite morphine, is detected in dark human hair transplanted to athymic mice after codeine administration. The codeine concentrations are greater than observed in albino rat hair at the same dose.

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COMPARISON OF HEROIN AND MORPHINE AFTER INHALATION AND I.V. ROUTES OF ADMINISTRATION.

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Inhalation of illicit drugs of abuse has dramatically increased in recent years. The purpose of the present study was to investigate the volatilization and pyrolysis of selected opioids, and evaluate the biodisposition and relative potencies of heroin and morphine after inhalation exposure and i.v. injection. Greater than 65% of heroin and codeine, while only 35% of morphine, was volatilized. The percentage of volatilization for each drug did not change with increasing doses. The antinociceptive ED_{50} values of morphine and heroin after i.v. administration in mice were 1.4 and 0.28 mg/kg, respectively, in the tail-flick procedure. However, inhalation exposure to 1 mg morphine and heroin produced 50% of antinociception in mice, suggesting they were equipotent by this route. In addition preliminary biodisposition studies demonstrated that the ED_{50} for inhaled morphine was 0.22 mg/kg, a dose comparable to the i.v. ED_{50} of heroin. Inhalation exposure to morphine and heroin resulted in more than 2-fold increase in the brain/body ratio of opioid equivalents from those obtained after iv injection. These data suggest that inhalation exposure to opioids results in a more potent antinociception than i.v. administration, possibly because of an enhanced bioavilability in the brain.

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SIMILARITY OF THE METABOLISM OF BUPRENORPHINE IN ANIMALS AND MAN

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Buprenorphine is a mu-opiate receptor partial agonist, kappa-opiate receptor antagonist which has been shown to be a safe and effective substitution agent in the treatment of opioid dependence. ADME studies have been carried out as part of the drug development program and have shown that the profile of metabolism is similar in animals and man. The ora1 absorption of unchanged buprenorphine is poor in man and animals due to extensive first pass metabolism but the sublingual route bypasses this allowing sufficient buprenorphine to be absorbed and to reach the brain; animal data show that the major species in brain is unchanged drug. The major metabolites of buprenorphine are the same in animals and man: N-dealkyl buprenorphine and its glucuronide conjugate and buprenorphine glucuronide conjugate. Excretion in animals and man is predominately via the feces in which the major species is buprenorphine probably due to intestinal hydrolysis of biliary-excreted buprenorphine conjugate. Buprenorphine and its conjugate appear in the urine at early times after dosing whereas N-dealkyl buprenorphine and its conjugate are renally excreted over a long period (>96h); in animals this was because of enterohepatic re-circulation of the metabolite.

EVIDENCE FOR CONVERSION OF HYDROCODONE TO HYDROMORPHONE BY RAT BRAIN

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Cytochrome P450s (CYPs) are present in rodent, canine and primate brain as demonstrated by catalytic, immunologic and molecular techniques. Brain CYPs appear to be regulated and expressed differently than hepatic CYPs. This suggests that not only the possibility of in vivo metabolism of drugs of abuse in brain, but also that the pattern of metabolism and hence activity may not be adequately reflected in plasma drug concentration measurements. Hydrocodone was incubated with the rat brain homogenates at 37°C for 90 minutes, and acetonitrile extracts of the incubation mixture were analyzed using an HPLC-electrochemical detector (ECD)/UV detector. There were two major metabolites observed by ECD, one of which was identified as hydromorphone by using the authentic compound. In contrast, four metabolites other than hydromorphone were found by sing the UV detector. Initial studies with rat liver microsomes demonstrated production of qualitatively and quantitatively different metabolite pattern. Studies to identify the metabolite produced in selected brain regions and to identify the cytochrome or other drug metabolizing enzymes responsible are under way. These results provide further evidence that the brain can metabolize drugs of abuse. Brain metabolism of hydrocodone could explain the lack of behavioral effect of inhibiting the peripheral conversion of hydrocodone to hydromorphone in rats that was previously reported by us (Joharchi N *et. al.,* CPDD 1994).

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COCAINE METABOLISM IN HUMAN LIVER MICROSOMES OF DIFFERENT AGES IS RELATED TO CYTOCHROME P450 3A FAMILY

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The N-demethylation of cocaine was studied in liver microsomes from human at different ages ranging from fetus, childhood to adulthood. In our incubation conditions only norcocaine was formed, neither cocaethylene, benzoylecgonine or hydroxynorcocaine was detected by gas chromatography coupled to mass spectrometry. The norcocaine formation was of similar rate in fetal specimens (757 ± 303.4 pmol/mg.min) and adult specimens (1366 ± 777 pmol/mg.min). Furthermore, the apparent Km values in fetal specimens (0.5 mM) showed higher affinity as compared to adult specimens (1.8 mM), their estimated intrinsic drug clearance were higher in fetal than in adults liver microsomes (0.037 ml/nmolP450.min, 0.0039 ml/nmolP450.min respectively). Catalytic activities at 1mM cocaine concentration showed good correlation with the immunodetected CYP3A proteins by means of Western Blotting, either in fetal specimens (r:0.87) or adult specimens (r:0.80). Inhibition studies using drugs well known as markers of CYP3A activity confirmed the major contribution of Cytochrome P450-3A. The results are of interest for the potential fetal toxicity risk that could take place in cocaine abuse at pregnancy. The high Km values found in adult livers are consistent with the fact that norcocaine is a minor metabolite found "in vivo" studies.

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PLASMA BUTYRYLCHOLINESTERASE ACTIVITY IN SUBSTANCE ABUSERS

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Plasma butyrylcholinesterase (BChE), synthesized in the liver, is the major cocaine-metabolizing enzyme in humans, and is known to metabolize heroin in vitro. Little is known about the factors that might influence BChE activity and its stability over time in substance abusers. We evaluated these issues in 153 subjects (127 men, 118 African American, 31 white, mean [SD] age 33.8 [6.2] years) who met DSM-IIIR criteria for substance dependence: 80 cocaine (including 23 with secondary alcohol abuse), 19 alcohol only, 12 heroin and/or marijuana, 21 nicotine only, and 20 non-addicted controls. Venous blood was drawn at study entry, when subjects were medication and drug-free and had normal liver function (AST/ALT ≤twice normal), and at 1, 6, and 12 months. Paired samples three days apart were drawn at each time interval. Plasma BChE activity was assayed in quadruplicate using the calorimetric method of Ellman, *et. al.,* (1961) with butyrylthiocholine as substrate. BChE activity was 2.11-7.13 U/L, with the range of published norms in non-substance abusers, and significantly correlated with body weight (r=0.18, p=0.03). There were no significant differences in enzyme activity by primary drugs of abuse, age, race, sex, or height. Enzyme activity did not change significantly over time (although sample size declined substantially, *e.g.,* no control subjects at 12 month interval), and was highly correlated between different time points.

MORPHINE-6-GLUCURONIDE: A POSSIBLE MEDIATOR OF ACUTE EFFECTS RELATED TO MORPHINE DEPENDENCE

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Morphine (M) is metabolized to morphine-3-glucuronide (M3G) and morphine&glucuronide (M6G). Both after single dose and repeated administration the concentrations of the glucuronides exceed that of morphine several fold. M6G binds to mu - and delta opioid receptors and could possibly contribute to the central nervous effects caused by morphine. In the present study we tested two hypotheses; (1) Whether M6G could cross the blood-brain-barrier (BBB), *in vivo,* and (2) whether systemically administered M6G could stimulate locomotor activity. M was given for comparison, and we used species (mice, rats) which do not form M6G from M. For study (1) microdialysis was used to sample M6G and M in striatal extracellular fluid after systemic administration in awake, freely moving rats (n=8). Serum and dialysate were sampled frequently during 120 min after equimolar s.c. drug administration and analyzed for M6G and M by HPLC. Serum AUC was ten times higher, and striatal dialysate AUC was three times higher for M6G than for M. In study (2) the locomotor response of C57 BL/6J mice (N=6-9 for each dose) to i.p. equimolar injections of M6G and M (3-80 pal/kg) was investigated. M6G increased locomotor activity from 1.3 to 2 times more than M. Pretreatment with mu-receptor and delta-receptor antagonists inhibited the locomotor response to both M6G and M. It was concluded that M6G could cross the BBB and mediate central nervous effects of importance to morphine dependence. Future studies might reveal the relative importance of the metabolite M6G in relation to M in the latter respect.

BLOOD-BRAIN BARRIER PERMEABILITY OF NOVEL OPIOID PEPTIDES USING *IN VITRO* CELL CULTURE AND *IN SITU* BRAIN PERFUSION METHODS

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Biphalin (Tyr-D-Ala-Gly-Phe-$NH)_2$ is a bivalent, opioid peptide that has structural similarities to enkephalins. Intracerebroventricular biphalin has been shown to be more potent than etorphine and morphine in eliciting antinociception, however after an intraperitoneal injection only a small fraction of biphalin enters the brain. To improve blood-brain barrier (BBB) uptake, halogenation (chloro and fluoro) of the phenylalanine residues was performed. Permeability coefficients (PC) cm/min x 10^{-4} ± S.E.M.; n=5-10) were calculated from passage across bonine brain microvessel endothelial cell (BMEC) confluent monolayers. The results show that the BMEC permeability of biphalin 55.00 ± 4.98 was improved 1.8 fold to 92.00 ± 5.88 upon chloro-halogenation. In contrast, fluoro-halogenation resulted in almost a two-fold decrease in BMEC permeability coefficient 23.21 ± 3.76. The enhanced BBB penetration from chloro-halogenation was further confirmed by using a well characterized *in situ* brain perfusion technique. CNS uptake of both biphalin and [P-Cl-Phe4,4']biphalin was expressed as the percentage ratio of brain to plasma activities (mean ± S.E.M. $ml.g^{-1}$). The uptake of [P-Cl-Phe4,4']biphalin into the brain (0.0897 ± 0.0182) was greater than that for biphalin (0.0583 ± 0.0019). These data suggest that chloro-halogenation of biphalin, an already potent analgesic, may improve BBB entry.

EFFECT OF HALOGENATION ON THE CNS ENTRY OF DPDPE

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[D-Pen^2, D-pen^5]enkephalin (DPDPE) is a *delta*-selective opioid peptide, which produces analgesia when given i.c.v. or i.th. However, since no analgesic effect is seen after s.c. administration, it has been inferred that DPDPE does not cross the blood-brain barrier (BBB). To improve the pharmacological characteristics of DPDPE, modification by halogenation was undertaken. The aim of this study was to compare the brain and CSF uptake of [^{3}H]DPDPE and two halogenated analogs ([^{3}H]p-Cl-phe^4 DPDPE and [I^{125}]p-Cl-phe^4 DPDPE) by means of a vascular brain perfusion technique in the rat. The results showed that the brain, but not the CSF uptake, of these peptides was greater than that of [^{14}C]sucrose, a vascular marker ($P<0.01$; Students t-test). Brain unidirectional rate constants (K_{in} $ul.min^{-1}.g^{-1}$±S.E.M.; n=4-6) were found to be 1.7 times greater for [^{3}H]p-C1-phe^4 DPDPE (4.26±0.22), than for [^{3}H]DPDPE (2.44±0.18) and Iodo, p-Cl-phe^4 DPDPE (2.52±0.29). This indicates that DPDPE and its analogs can cross the BBB, but at different rates. The blood-CSF barrier playing only a minor role in the brain uptake of these peptides. However, while the presence of two halogens has no significant effect, chloro-halogenation improves the ability of [^{3}H]DPDPE to enter the CNS. It is not known whether this is related to the presence of the iodo-group itself, or to its' position on the tyrosine-^{1} group of p-Cl-phe^4 DPDPE.

AIDS-RELATED KNOWLEDGE AND HIGH-RISK BEHAVIORS OF PREGNANT DRUG-DEPENDENT WOMEN

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This preliminary study investigated (a) AIDS-related knowledge, (b) engagement in high-risk behaviors, and (c) relationships between AIDS-related knowledge, high-risk behaviors, and sociodemographic characteristics of 41 pregnant women dependent **on** cocaine or opiates who entered treatment. At treatment entry, patients completed self-report questionnaires on AIDS-related knowledge and sexual and drug use practices. Awareness of AIDS-related risk factors varied: There was a high rate of understanding of risk associated with drug use and of perinatal transmission of HIV. However, only 55% recognized the potential for transmission of HIV to the newborn via breastfeeding. Knowledge of high risk sexual behavior varied, and knowledge of the medical consequences of HIV was low. Engagement in several high-risk behaviors were identified: lack of condom use by sex partners (93% in last month); intravenous drug use (46% lifetime); sharing of needles (24% in past year); sex with an injecting drug user (35% in past year); and exchanging sex for money or drugs (37% in past year). AIDS-related knowledge and engagement in high risk behaviors were not significantly correlated. Implications of these findings for developing effective HIV prevention strategies in this population are suggested.

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PSYCHOLOGICAL DIFFERENCES BETWEEN PERINATAL SUBSTANCE ABUSE TREATMENT ACCEPTORS AND REJECTORS

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Do perinatal substance abusers self-select a treatment matched to their psychopathology levels? This study compared the addiction and psychological characteristics of 109 female substance abusers who accepted intensive outpatient perinatal substance abuse treatment to 26 “treatment rejectors” who accepted research followup. Despite demographic similarity between groups, acceptors evidenced more addiction severity on the ASI and greater psychopathology on the MCMI-II, MMPI-2, and SCL-90-R than did rejectors. Eighty percent of acceptors and 54% of rejectors were primary crack cocaine abusers; 7% of acceptors and 23% of rejectors were primary heroin abusers. MMPI-2 mean profiles differed; the acceptors’ mean profile was a 4-8, while the rejectors’ mean profile was a 4-9. Cluster Analysis (Ward’s Technique) revealed subgroups with severe psychopathology, mild character pathology, and normal range profiles on both the MMPI-2 and the MCMI-II. Three-fourths of the acceptors but none of the rejectors had severe psychopathology on the MMPI-2. Sixty-two percent on rejectors had normal range profiles on the MMPI-2. Treatment self-selection occurs at least partly as a function of addiction severity and psychiatric severity, such that women with less pathology reject intensive treatment. Cluster analysis is helpful in revealing psychopathologically homogeneous subgroups of substance abusing women.

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TREATMENT OUTCOME AS A FUNCTION OF CLUSTER MEMBERSHIP

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Subjects were 37 polysubstance abusing women (SCID dx: 90% cocaine, 47% ETOH, 44% cannabis, 21% opioids) who participated in 20 weeks of intensive outpatient treatment. The sample was mostly single (79%) and African American (84%) with a mean age of 27 years. Psychological assessment was conducted at Intake and Ward's Cluster Technique was used to identify homogeneous sub-groups. Three (3) distinct clusters, reflecting mild, moderate, and severe psychopathology, were derived for each of the four tests considered (MMPI-2, MCMI-II, SCL-90-R, and ASI). The nonparametric Sign-Rank Test was used to determine whether median scores differed between Intake and Week 20. Subjects in the "Severe" group evidenced the greatest change on all four tests. Specifically, they improved on 8 of 10 MMPI-2 scales, 13 of 22 MCMI-II scales, all 11 SCL-90-R scales, and 5 of 7 ASI domains (all except legal and employment). Subjects in the "Moderate" group improved on 1 MMPI-2 scale, 10 SCL-90-R scales, and 3 ASI domains (drug, alcohol, and psychiatric). On the MCMI-II, three scales improved and two (Aggressive/Sadistic and Paranoid Personality Disorders) worsened. Subjects with "Mild" pathology improved on four MMPI-2 scales and two ASI domains (drug and family/social). Although they did not improve on either the MCMI-II or the SCL-90-R, scores on these tests were not elevated to begin with. We conclude that homogeneous sub-groups exist in the female addict population. Cluster analytic techniques may have utility in treatment outcome and treatment matching studies.

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BEHAVIORAL AND PSYCHIATRIC CHARACTERISTICS OF ADOLESCENT FEMALES IN RESIDENTIAL DRUG TREATMENT

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Research on adult women in therapeutic communities (TCs) for the treatment of substance abuse problems has shown that women enter treatment with more severe psychopathology than their male counterparts, but that they require shorter treatment tenures to achieve more favorable post-treatment outcomes. There have been few if any studies which have reported on the psychiatric profiles of adolescent, drug abusing females in residential treatment. The current research presents the findings on 220 females admitted to four residential TCs for the treatment of substance abuse and related problems. The Diagnostic Interview for Children and Adolescents (DICA-R) was used to assess the prevalence of psychiatric disorders, and behavioral indicators of disturbance (*e.g.,* measures of social adjustment, peer deviancy, school problems) were obtained with an extensive psychosocial interview. A large majority of females (80%) has multiple diagnoses in addition to their substance use/abuse. Results show that a significantly greater proportion of females than males yielded psychiatric disorders across all categories of disturbance - developmental, affective and anxiety. Of note is that gender differences for developmental disorders, *i.e.,* Conduct Disorder, Oppositional Defiant Disorder and Attention Deficit Hyperactivity Disorder, is in contrast to that reported clinical and community samples. Implications for treatment process, retention and outcome are discussed.

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WOMEN'S PERCEIVED BARRIERS TO COMPLETION OF DRUG TREATMENT

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This study was designed to assess barriers to completing treatment as perceived by women enrolled in a therapeutic community. A convenience sample of women (n=50) was interviewed at six month follow-up regarding satisfaction with treatment. For this study, open-ended questions that might present barriers to treatment were selected for review. Demographics for the group shows the average age as 35 with most of the women (64%) having completed high school. A majority was African-American (69%), 20% were white and 10% Latina. For the entire sample (n=50), groups were most often cited as 'most helpful' (58%). while specific confrontation techniques (*e.g.,* yelling, screaming) were given as 'least helpful' (40%). Ninety-four percent stated they were generally satisfied with treatment services received, and most (74%) said they would seek help again at this program. Of those who would not consider coming back (26%), dissatisfaction with some confrontation techniques was again given as the primary reason. Many women (68%) left within the first six months of treatment. Nearly 75% left by choice and 18% were expelled. The primary reasons these women (n=29) gave for leaving treatment related to approaches involving strong verbal reprimand and specific confrontation techniques (26%) which they described as "yelling", "screaming", "scare tactics", or "pressure". Few women said they left due to childcare or family issues (9%). For women entering a therapeutic community, certain treatment approaches involving strong confrontation appear to represent barriers for women in drug treatment.

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DIFFERENCES BETWEEN WOMEN-ONLY AND MIXED-SEX DRUG TREATMENT PROGRAMS IN LOS ANGELES COUNTY

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The goal of this study was to compare the characteristics of drug treatment programs that provide services only to women with those that threat both men and women. A comprehensive survey of drug treatment programs in Los Angeles County was conducted from December 1992 to March 1994. A total of 294 programs responded to the survey, for a response rate of 83%. Of 199 residential and drug-free outpatient programs, 34 provided services to women only and 165 to both sexes. Women-only programs were less likely to provide individual therapy (79% versus 93%, $p<.05$) or couple therapy (74% versus 90%, $p<.05$) and were more likely to include peer advocacy (100% versus 66%, $p<.05$), on-site 12-Step meetings (88% versus 63%, $p<.05$), and advocacy by case managers (94% versus 80%. $p<.05$). They were also more likely to offer job skills training (44% versus 26%, $p<.05$), training in anger management (100% versus 84%, $p<.05$), transportation assistance (65% versus 35%, $p<.05$), housing assistance (59% versus 26%, $p<.05$), and social outings (100% versus 49%, $p<.05$). They were significantly more likely to offer a variety of services related to parenting and childcare, to describe their programs as highly demanding of clients, and to deliver treatment in phases. Lastly, women-only providers were more likely to accept payment through state funding (Medi-Cal) (100% versus 73%, $p<.01$) and less likely to either charge a fee for service (62% versus 90%, $p<.01$) or to accept payment through private insurance (24% versus 66%, $p<.01$).

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THE EFFECT OF SOCIAL NETWORKS AND RELIGIOSITY ON SUBSTANCE USE AMONG WOMEN

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We hypothesized that women with strong religious convictions and little knowledge of friends, relatives, and/or colleagues who use alcohol or drugs would be less likely to use substances themselves. Data were obtained from an anonymous nationwide mailed survey of registered nurses, and these analyses were restricted to all women under age 45 (N=2395). This hypothesis was supported both for respondents reporting heavy alcohol use, and any marijuana/cocaine use in the past year. Religiosity was measured using a four item scale modified from Rohrbaugh and Jessor (alpha=0.90). Highly religious women were six times less likely to use marijuana or cocaine and three times less likely to drink heavily (5+ drinks/occasion). Knowledge of others who drank heavily was only mildly related **to** personal heavy alcohol use (O.R.=1.7) but knowledge of others who used marijuana or cocaine was highly related to personal use of marijuana or cocaine (O.R.=20.6), when adjusted for age, race, education, urbanicity and marital status. Involvement in peer networks that engage in substance use and related deviant behavior has been shown to be related to adolescent drug use. This work extends those findings to an adult sample of women by suggesting that social networks continue to influence substance use into adulthood.

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PITUITARY ADENOMAS IN FEMALE DRUG ABUSERS: CASE STUDIES

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Two cases of pituitary adenomas were observed in females who were dependent on drugs. One patient (LD) described a history of amenorrhea for live years. CT-Scan documented a pituitary microadenoma. Prolactin levels were about 1.5 limes above normal. The treatment for elevated prolactin levels was bromocriptine; one year later, menses resumed and prolactin levels were about 1.5 times normal. The other patient (BW) periodically complained of blurred vision. CT-Scan and MRI documented a substantial pituitary macroadenoma. The tumor was partially removed at another facility and radiation therapy was administered. Since her discharge from the unit 19 months ago, LD was drug-fee except for using cocaine for a six month period. Since her discharge from the unit 18 months ago, BW was drug-free except for using heroin twice. We conclude that when evaluating patients who abuse substances, it is important to carefully consider all patients' complaints because some of them may not be due to withdrawing from drugs.

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THE IMPACT OF SEXUAL ABUSE ON DRUG TREATMENT

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Persons unable to eliminate or control their drug use despite numerous treatment attempts, may be influenced by a history of sexual abuse. One hundred and thirty women opiate users (N=48 from methadone maintenance treatment programs and N=82 from needle exchange programs (N=82) in New York City) were interviewed to determine if women with sexual abuse histories respond less successfully to drug treatment than those without. Sixty-eight (52%) women reported a history of sexual abuse. They were two times less likely lo be in current drug treatment (p=.07), but twice as likely to have had more than one treatment attempt (p=.06). They also reported more cocaine use (p=.09), speedball use (p=.03), and drug injection (p=.03) in the past six months. Women with sexual abuse histories were more likely to report maternal sexual abuse (p=.04), participation in sex work (p<.001), and HIV seropositivity (p=.07). Women with sexual abuse histories had multiple drug treatment attempts and more severe and diverse drug use patterns. Efforts should be made to identify these women and to intervene in order to minimize the risk of subsequent harm.

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TREATMENT OF FOUR PREGNANT HEROIN ADDICTS WITH BUPRENORPHINE; HISTORY AND OUTCOME

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Four heroin addicts who were in treatment at the time of pregnancy received buprenorphine sublingually for the entire duration of their pregnancy. The treatment enabled these four patients to stop a daily intake of heroin between 1/10 gram and 1 gram, taken intravenously, intranasally or by smoking. The doses of buprenorphine used during pregnancy were between 1 mg and 1.5 mg per day. Three patients staled that they had taken some heroin during the first three months, two said they had taken some between the third and sixth months and none during the last three months. All the pregnancies and deliveries were normal, taking place between the 39th and 41st week. The babies weighed between 2.9 kg and .5 kg and the Apgarscores were 9/10/10 in all four cases. None of the babies presented withdrawal symptoms. One of them appeared in an agitated state at 13 days, which could be attributed to withdrawal from buprenorphine. The children have all developed normally so far and are today between three and five years of age. If it is confirmed that newborns of mothers treated with buprenorphine have less withdrawal symptoms than those treated with methadone, it might be appropriate to switch from methadone to buprenorphine during pregnancy (preferably between the third and sixth month). The doses of buprenorphine we used five years ago were considerably lower than those used in current therapeutic experiments. Higher doses would probably have made it possible to reduce heroin use even more during pregnancy. However, the eflects of higher doses on the new born babies should be compared with our results.

CHANGES IN METHADONE HALF-LIFE DURING PREGNANCY

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In an on-going pilot study of methadone metabolism during pregnancy, we have tapered seven women from methadone during their last two trimesters of pregnancy. The women have been hospitalized during this ten day two week procedure and have been monitored carefully for use of drugs other than methadone. All the women were essentially healthy, other than their addictive diseases, and none of the fetuses appeared to have significant anomalies or growth retardation. During the hospitalization, the women were given once-daily doses of methadone. Blood was drawn for methadone levels immediately before (C_1) and two hours after (C_2) the daily dose. Levels were measured by gas chromatograph mass spectrometer. Women will be recruited from the local methadone clinic who are not pregnant, and who will go through a similar taper to form a control group. The half-lives will be calculated based on a one-compartment pharmacokinetic model and the pregnant and non-pregnant samples will be compared using a t-test. $C_1 = C_2 e^{-kt}$ $.693/k = t_{1/2}$ t is the time between samples. **k** is the elimination rate constant and the half-life is $t_{1/2}$.

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PRELIMINARY REPORT ON EKG ABNORMALITIES IN PREGNANT ADDICTS

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Since both cocaine and heroin have been shown to produce EKG alterations, we examined the EKG records of pregnant addicts for evidence of abnormalities. Records of patients abusing primarily cocaine (COC, n = 43), cocaine and heroin in combination (C+H, n = 52) and polydrug (POLY, n = 36) abusers were examined. The following table shows the percentage of abnormal EKGs (ABN) for the three groups. The abnormal EKGs were further divided into those where PR interval shortening (PR), abnormal ST segments (ST), left ventricular dilatation (LVH) or heart block (HB) was observed.

Group	Age	DDD	GA	Race	ABN	P R	ST	LVH	HB
COC	27±1	4.6±.4	26±1	88	40%	36%	27%	23%	14%
C+H	27±1	6±1	22±1	79	42%	26%	22%	30%	22%
POLY	26±1	6.3±1	23±1	78	31%	33%	42%	8%	17%

The gestational ages (GA) and the percentage African Americans (Race) were similar for the groups. A surprisingly large number of pregnant addicts showed some type of abnormality. Duration of drug dependence (DDD) was always longer for those addicts demonstrating an abnormality, suggesting that duration of drug use may be a critical factor in the development of EKG changes. The type of abnormality was similar across groups, with the exception of LVH, which appeared less frequently in the polydrug abusers, and ST, which occurred more frequently in the polydrug abusers. Since less than 50% of the polydrug abusers used cocaine, cocaine abuse might contribute to the appearance of LVH. The results of this study, while requiring further confirmation, do indicate that abnormal EKGs are common among pregnant addicts.

OBSTETRIC AND ANESTHETIC OUTCOMES IN CHRONIC COCAINE ABUSING PARTURIENT

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Maternal cocaine use is associated with an increase in obstetric and perinatal morbidity. Obstetric and anesthetic complications of maternal cocaine use were examined in 169 subjects who underwent cesarean section. Four groups of subjects were defined: a control-group (never used any drug including ETOH and tobacco, N= 103); and three cocaine groups (parturient who used cocaine in the past but not during this pregnancy; parturient who used cocaine during this pregnancy; parturient who used cocaine immediately prior to delivery, N= 66). Among cocaine users, the following complications were significantly more common: placental abruption (20%), placenta previa (7%), premature rupture of membranes (6%), and hypertension (8%). General anesthesia in the cocaine abusing subjects had to be supplemented significantly more with intravenous agents, and induction of spinal anesthesia was associated with hypotension significantly more often in the cocaine groups. Overall, cocaine abusing subjects who underwent general anesthesia were less hemodynamically stable than the control groups. Fetal distress and poor Biophysical Profile (BPP) occurred more often in cocaine users. Upon delivery, meconium staining of the newborns was significantly more common in the cocaine groups. Inner-city parturienr who abuse cocaine and require a c-section are at greater risks for multiple obstetric and fetal complications.

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EVALUATION OF COMPREHENSIVE SERVICES TO MOTHERS WITH COCAINE-EXPOSED INFANTS

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The Family Rehabilitation Program (FRP) is a new New York City-wide program that provides a unique combination of intensive family preservation services and drug abuse treatment to parents with in-utero cocaine-exposed newborns reported to the child protection system. FRP is designed to meet the special service needs of mainly minority-group, cocaine/crack-dependent women with drug-exposed infants and young children who have been underserved by the traditional drug abuse treatment system. Services are provided by community-based voluntary agencies selected for their ability to provide culturally sensitive services. Special efforts also are made to involve extended family members and significant male figures in case management. The study reports prelimitnary results from a process and outcome evaluation of FRP. Current data are from 14 agencies involving 386 families whose cases were active in July 1993. One year later, 55% had positive outcomes, as defined by case closing with achievement of case goals or, if still active, decreased risk of child foster care placement. Foster care was averted in 93% of the families and 10% had a child returned from foster care. FRP is a promising intervention with this population.

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SHORT TERM OUTCOME OF COCAINE DEPENDENT WOMEN TREATED IN INPATIENT AND OUTPATIENT SETTINGS

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Although, there is mounting evidence that treatment process and program service variables can affect treatment outcome there is controversy regarding whether one form of treatment is superior. A comparison of the effectiveness of an inpatient vs. day hospital program for male cocaine abusers found no significant differential reduction in use of cocaine in subjects over seven months (Alterman, *et al.,* 1994). There have, however, been no investigations of the differences between women cocaine addicts treated in inpatient and outpatient settings, This study examines baseline and short term outcome (2 and 6 month) differences between 50 cocaine addicted women treated as outpatients and 50 women treated as inpatients. The only significant baseline differences found were that inpatient women reported more use of cocaine and alcohol, more suicidal thoughts and attempts, but fewer employment problems than outpatient women in the month prior to entering treatment. Inpatients were also more likely to be diagnosed with major depression (44% vs. 22%) or obsessive compulsive disorder (8% vs. 0%) than outpatients. No significant differences in cocaine use as found in urinalysis or self report measures was found between the two groups at either the two or six month follow up point. By the two month follow up, however, 50 % of each group had relapsed. There was no evidence of differential improvement on any ASI composite score in the two groups over six months.

BLACK WOMEN'S PATHWAYS TO ILLICIT DRUG DISTRIBUTION AND USE

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Using a small sample of women crack sellers in New York City, this ethnographic analysis documents how low-income black women gain access to the male-dominated labor market of illicit drug sales. Pathways to regular involvement include lack of legitimate opportunities, deviant lifestyles among kin, and participation in street life as teens. As young adults, these women have limited and unsuccessful formal labor force participation, engage in hustling to earn income, enjoy "partyin" but have few legal options. The importance of structural conditions in the neighborhood is central to their past and current criminal involvement.

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MOTIVATION AND READINESS FOR TREATMENT IN A SUBSTANCE USING POPULATION

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As part of a study on Treatment Utilization and Effectiveness (TUE), 3,786 persons were surveyed at jails, hospital emergency rooms (ERs), and sexually transmitted disease (STD) clinics in Los Angeles County from 1992 to 1994. Subjects who reported use of an illegal drug in the past year were asked to participate in the longitudinal aspect of the TUE study, which involves yearly follow-up interviews for a randomly selected group of participants.

As of April, 1995, 327 subjects had been interviewed at one year follow up. All were administered an instrument on Motivation and Readiness for Treatment (M&R). The M&R is a modification of an instrument designed by Simpson (1992) as part of the Drug Abuse Treatment for AIDS Risk Reduction (DATAR) project. Scales were developed to assess Perceived Drug Use Problems, Desire for Help, Treatment Readiness, and Self Efficacy. Preliminary findings indicate that on average, subjects currently in treatment (N=27) or ever in treatment (N=149) scored significantly higher than the rest of the sample on Perceived Drug Use Problems, Desire for Help, and Treatment Readiness. There was no difference in Self Efficacy. Similarly, subjects reporting heavy drug use scored significantly higher on these scales than those reporting moderate use.

LONG TERM OUTCOMES OF CLIENTS ENTRING A DAY TREATMENT PROGRAM

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This study evaluated outcomes over 18 months for clients (N=66) entering a drug abuse day treatment program (DT). Baseline (BL) interviews were conducted at approximately two weeks after admission. Sixty-four percent of the sample were later transferred to the residential program (RT). Data was collected at all time points (BL, 6, 12, and 18 months) on 46% of the sample, and included the Addiction Severity Index (ASI), Beck Depression Inventory (BDI), and Symptom Checklist 90R (SCL-90R). Population demographics include mean age 33.1 years; mean education 12.3 years; 18% women; and ethnicity: 53% African American, 35% white, 6% Latino/a, and 6% Asian. MANOVA techniques were used to compare outcomes of those followed across all time points, and across the three follow-up periods (6, 12, and 18 months). Improvements occurred between baseline and six months, and were maintained up to 18 months in the ASI legal, drug, alcohol, social composite scores. Clients showed gains at six months in BDI and SCL-90R scores, followed by a worsening of symptoms at 12 months, then renewed improvement at 18 months. Employment showed no change from baseline to six months, but steady gains from 6 to 18 months. This study suggests that DT, either as a single modality or in combination with RT, can attract and treat clients with diverse demographic and addiction backgrounds resulting in significant and durable improvement.

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A RANDOMIZED TRIAL OF DAY TREATMENT: SIX MONTH OUTCOMES

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This study was designed to assess the effectiveness of an intensive day treatment (DT) program in comparison with residential treatment (RT). Five hundred and thirty-four clients were randomly assigned to either DT or RT. Homeless clients, and those referred by the criminal justice system specifically to residential treatment, were excluded. Those who remained in treatment through a two week "wash-out" period were enrolled, resulting in DT (n=123) and RT (n=159) cohorts. Participants were interviewed at baseline and six months using the ASI, the Beck Depression Inventory (BDI), and a social support measure. The two cohorts did not differ in terms of demogmphics, and retention in DT (mean=19.8 weeks) was similar to that in RT (mean=18.5 weeks; t=0.63, p=0.53). The cohorts differed on three of nine outcome variables measured at baseline, such that DT clients had fewer psychiatric symptoms and greater social support. After six months, 82% of clients were re-interviewed. Both groups showed improvement from baseline to follow-up on ASI composite scores for alcohol, drug, medical, legal, and social problem severity, and on the BDI. To assess whether clients in either program achieved better results, we cornpared mean scores at six month follow-up using ANCOVA to control for the baseline level of each outcome. Comparison of least square means at six months for each outcome, by group, showed that both groups achieved the same level of treatment gain. Level of improvement differed only for the alcohol composite score, such that DT clients had lower alcohol problem severity on follow-up. Important subsets of clients were excluded from study, and this qualifies interpretation of results. Among clients randomly 'assigned, both groups showed significant treatment **gains** at six month follow-up, and the level of change achieved did not differ significantly between groups. **In** this sample, day treatment was as effective as residential treatment in improving client outcomes up to six months post-admission.

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CLIENT SATISFACTION FOR INDIVIDUALS RANDOMLY ASSIGNED TO TREATMENT MODALITY

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This study assesses client satisfaction with the treatment modalities to which they were randomly assigned. A total of 282 clients were randomly assigned to either a residenlial (RT) or day treatment (DT) therapeutic community for substance abusers. Of lhose interviewed at six months, 31% were female, 57% African American, 25% White, 14% Latino/a. with a mean age of 34 years. At six months, 82% of clients (n=232) were re-interviewed and asked about treatment satisfaction. Nearly half (49%) were assigned to DT. For both DT and RT groups, over 70% were 'mostly' to 'very' satisfied with their program and 90% of the both groups would recommend the same program lo a friend. A subset of 232 clients (n=168), was asked additional questions regarding treatment preference and satisfication with the treatment modality to which they were randomly assigned. When asked about original treatment preferences at admission, significantly more clients had preferred residential over day treatment for both groups [chi sq.=9.0, p<.01] However, at six months, while satisfaction with overall treatment was high for both groups, significantly more DT clients (87%) than RT clients (72%) were satisfied with their assignment [chi. sq. = 4.6, p<.05] When asked which modality clients would choose at six months, over half of both DT (68%) and RT (57%) would choose the same treatment modality. Differences in treatment preferences occurred upon admission; at six months, however, both groups expressed high satisfaction with assigned treatments suggesting that quality of treatment services for both DT and RT was comparable.

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DRUG TREATMENT COUNSELOR PERCEPTION OF CLIENT CHANGEABILITY

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There is extensive research concerning the effects of an individualís locus of control on health outcomes. However, research on how health-caregivers influence a patientis locus of control has been sparse.

As part of a larger study investigating drug treatment counselorsí practices and effectiveness, locus of control is being investigated in two ways: (1) through an assessment of counselor attitudes about the feasibility of client recovery (client changeability), and (2) through an assessment of client locus of control. Counselor attitudes are being investigated using the Client Changeability Scale (CCS). To create this scale, we extensively modified the Drinking-Related Locus of Control Scale to assess the extent to which counselors believe that clients have control of their substance abuse behavior and recovery. A draft of the CCS was pre-tested with practicing counselors, resulting in many refinements. The final version of the scale will be administered to approximately 240 counselors in 40 drug treatment programs in Los Angeles County. Preliminary results from approximately 75 counselors will be presented.

In the next phase of the study, a parallel scale will be developed for assessing clientsí attitudes toward their substance abuse and recovery. Client locus of control will be assessed using the Drug-Related Locus of Control Scale (DRLCS). We will examine the relationships between counselor beliefs about the ability of clients to control their abuse of drugs and client drug-related locus of control, and how the two, independently or interactively predict clientsí long-lerm treatment success.

DRUG TREATMENT COUNSELORS--PRACTICE AND EFFECTIVENESS

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As part of a larger study to improve understanding of the drug treatment process, a survey is being conducted of counselors in 40 drug programs in Los Angeles County. The 40 programs were selected to represent five major modalities: inpatient hospital, day treatment, residential, outpatient drug-free, and methadone maintenance. The self-administered instrument includes items on counselor background and training, psychological health, job activities, therapeutic belief and approach, counselor burnout, self-efficacy, decision-making and career goals, counselor job satisfaction, conflict experienced in the workplace, supervisor and co-worker support, locus of control, and caseload. Clinical records of clients of these counselors are being abstracted, which will provide a limited base for evaluating counselor effectiveness.

WILLINGNESS TO PARTICIPATE IN A "MATCHED" REFERRAL TO DRUG TREATMENT

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From December 1993 to May 1995, 619 subjects recruited for interview by two research studies of illicit drug users were screened for eligibility for participation in the Matching Project. After excluding those who were not eligible because they were currently in treatment, considered themselves ìc lean,î were incarcerated, or did not meet other Matching Project subject criteria, 289 subjects were offered the option of an additional interview with the Matching Project that would result in a ìmatchedî referral to a drug treatment program in Los Angeles County. Information has been assembled to investigate any differences between those who opted for the matching interview and those who did not. Study A asked 64 subjects and 38 (59%) agreed to do the matching interview for referral to a drug treatment program. Study B asked 225 subjects and 51 (23%) agreed to participate in the matching interview. Analysis of the differences between those who agreed to the matching interview and those that did not included the following variables which were available for both data sets: age, gender, ethnicity, primary drug of abuse, and previous involvement in drug treatment programs. It is hoped that this information will lead to a better understanding of readiness for drug treatment and improved outreach efforts.

ACKNOWLEDGEMENTS:

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THE "PAVED WAY"; EFFECT OF LINKING IN-TREATMENT ADDICTS WITH 12-STEP PROGRAM VOLUNTEERS

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Although it has generally been difficult to complete research within 12-step fellowship groups, there exists a strong need to measure the effectiveness of this mutual-help approach to recovery. Additionally, the need for a clinically effective as well as cost effective way to provide some level of individual attention has not been adequately addressed in the substance abuse treatment field. One solution includes the involvement of recovering addicts to allow for a "paved-way" into the 12-step fellowships, and provide increased individual attention. This study proposes random assignment of 50 clients into two groups, half getting a "paved-way" protocol in addition to intensive outpatient treatment. The Addiction Severity Index will be administered to subjects at baseline, and 60-day follow-up. Those in the "paved-way" protocol will be matched with recovering volunteers who have agreed to take the subject to three different 12-step recovery meetings. After 60-day follow-up, change differences in the groups will be examined, exploring treatment completion rates, maintenance of sobriety, involvement in 12-step fellowships, medical, employment, drug, alcohol, legal, family, and psychiatric problems. Preliminary data from this study will be presented. It is expected that individuals participating in the paved way protocol will show increased rates of recovery and decreased difficulties in these areas.

WHAT TREATMENT SERVICES DO DRUG USERS CONSIDER IMPORTANT?

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As part of a larger study on matching drug users to treatment programs, an instrument has been developed for assessment and treatment referral. The main objective of one portion of this instrument is to ascertain client preferences with regard to program characteristics and services provision. The instrument was pilot tested at several social service programs. This paper will report on the service preferences of subjects interviewed in a methadone maintenance clinic, a residential drug treatment center, and a homeless shelter in Los Angeles County. Relevant items of the instrument include ratings of the importance of: various counseling approaches, medical services, social skills programs, child care and other ancillary services and treatment modality. Analysis will examine the relationship between client characteristics (race, gender, primary drug of abuse, insurance status, needs and problems in various domains) and treatment service preferences. The instrument is currently being computerized for use in conjunction with a treatment provider database to facilitate efficient matched treatment program referral.

PREDICTING PERCEIVED QUALITY OF DRUG TREATMENT FACILITIES USING LATENT VARIABLE MODELS

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Key personnel in 294 drug treatment facilities in Los Angeles County were surveyed to provide objective program information and subjective evaluations of various aspects of their treatment programs. These ratings were obtained as part of the UCLA Drug Abuse Research Center Treatment Referral Network Survey which has the goal of matching drug users' treatment needs to appropriate services. Using latent variable models, a subset of the measures was used to predict perceived quality of the treatment programs. Perceived Quality was indicated by ratings of the effectiveness of counseling services, staff, and overall program. At the latent variable level, significant predictors of Perceived Quality included a Programmatic Focus (philosophy and emphasis), and Program Intensity (greater frequency and number of psychological and social services). Group Therapy and Methadone Program (including detoxification and maintenance) had significantly negative effects. Individual Therapy had a slightly positive but not statistically significant effect on Perceived Quality. There were also significant relationships among measured variables: More individual counseling and a skills-building approach predicted higher ratings of overall program, supportive group therapy predicted higher ratings of treatment staff, and a change-oriented emphasis predicted higher ratings of counseling services. Measured variables representing staff turnover ratio, caseloads, and ratio of licensed staff to total staff did not significantly predict quality and did not increase the amount of variance accounted for by the final path model. The variables were, however, significantly correlated with some of the predictors which in turn predicted quality.

THE IMPACT OF MULTIPLE EPISODES OF OUTPATIENT DRUG TREATMENT ON PARTICIPATION IN TREATMENT

J. M. Hawke

National Development and Research Institutes, Inc.

Building on earlier analyses of the determinants of retention and client participation in treatment among probationers who are mandated to drug treatment in New York City (Hawke and Falkin, 1994; Hawke, 1994). this study explores how characteristics of previous treatment episodes impact on the clients' current participation. Descriptive statistics indicate that about six percent of probationers ever succeed in contracted drug treatment. Paired t-tests indicate that the levels of treatment participation in the first episode of treatment is related to subsequent treatment participation and a logistic regression shows that probationers who are not active cocaine users when they enter treatment and who exhibit higher levels of participation are much more likely to succeed in treatment the first time around.

Opinions expressed in this paper may not represent the opinions of the U.S. Government, the New York City Department of Probation, the Medical and Health Research Association of New York City, Inc. or the National Development and Research Institutes, Inc..

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MAXIMIZING COST EFFECTIVENESS OF MEASURING TOTAL PLASMA METHADONE LEVELS

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Plasma concentration of methadone is a useful tool in the treatment of opiate addicts in methadone matintenance programs. Standard measurement employs gas chromatography/mass spectrometry (GC/MS), a costly, time consuming procedure. Nineteen volunteer methadone maintenance patients provided blood samples to enable a comparison of standard GC/MS methadone concentration measurement to Abbott Laboratories Fluorescence Polarization Immunoassay (FPIA) technology (ADx). The correlation proved strong (r = .895; 1.0057 x FPIA result + 17.4088 = GC/MS result). Comparing independent laboratory GC/MS costs and on-site FPIA cost resulted in a savings of more than 75%. These data suggests that FPIA technology is an accurate, practical, and cost efficient means of measuring a total plasma methadone level.

THE EFFECTS OF DEZOCINE IN METHADONE-MAINTAINED VOLUNTEERS

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Dezocine is an opioid mu partial agonist approved for use as an analgesic in the United States, The purpose of this study was to characterize the effects of dezocine in comparison to naloxone, hydromorphone, and placebo in six volunteers maintained on methadone (30 mg p.o. daily). In a residential laboratory participants underwent pharmacologic challenges two to three times per week. Challenges were given 20 hours after methadone and consisted of a double-blind i.m. injection of: dezocine (dose range 7.5 - 60 mg), hydromorphone (5 and 10 mg), naloxone (0.1 and 0.2 mg) or saline. Measures included physiologic indices, and self-reports and observer ratings of drug effects. Naloxone and hydromorphone produced characteristic antagonist-like and agonist-like effects, respectively. At intermediate doses (30-45 mg) dezocine produced antagonist-like effects, with significant elevations of subject visual analog scale ratings of Drug Effects, Bad Effects and Sick, and of observer ratings of restlessness, yawning, and the scores on opioid withdrawal scales. The specific profile of effects produced by dezocine differed from that produced by naloxone, and dezocine exhibited a bell-shaped dose-response curve for antagonist effects. These results suggest either that there also may be non-mu effects produced by dezocine, and that at higher doses these non-mu effects modulate and attenuate the mu opioid effects produced, or that at higher doses dezocine's mu agonist activity is sufficient to outweigh its antagonist effects.

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EFFECTS OF BUTORPHANOL, HYDROMORPHONE, AND NALOXONE IN HYDROMORPHONE-MAINTAINED VOLUNTEERS

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The purpose of this study was to examine the effects of the opioid mixed agonist-antagonist butorphanol in comparison to naloxone (an opioid antagonist), hydromorphone (an opioid mu agonist), and saline in hydromorphone-maintained volunteers. Volunteers were eight opioid-dependent adults (two female, six male) who resided on a clinical research ward throughout the study. Volunteers were maintained on hydromorphone, orally administered daily in four 5 mg doses (20 mg/day total). Pharmacologic challenges were administered two to three times per week and consisted of double-blind intramuscular injection of: butorphanol (0.375, 0.75, 1.5, 3 and 6 mg), naloxone (0.1 and 0.2 mg), hydromorphone (5 and 10 mg), or saline placebo. Injections were administered three hours after the last dose of hydromorphone and effects were assessed in three hour experimental sessions. Physiologic measures and subject- and observer-rated behavioral responses were measured before dosing and for 2.5 hours after drug administration. Peak change from baseline analyses revealed that hydromorphone significantly decreased pupil diameter, and significantly increased subject-reported visual analog scale ratings of "Good Effects", "Liking", and "High". Naloxone significantly increased ratings of both "Bad Effects" and "Sick". Thus the procedures used in this study were sensitive to detecting both agonist and antagonist effects (controls). Butorphanol demonstrated neither agonist-like nor antagonist-like effects suggesting that butorphanol has low abuse potential and low potential for precipitating opioid withdrawal in volunteers maintained on this dose of hydromorphone.

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NALOXONE DISCRIMINATION IN OPIOID-DEPENDENT HUMANS UNDER A NOVEL-RESPONSE DISCRIMINATION PROCEDURE

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The major aim of this study was to develop a human laboratory model for examining opioid withdrawal-like effects; *i.e.,* an opioid antagonist drug discrimination procedure in opioid-dependent humans. Methadone-maintained subjects (25-55 mg/day) were trained to distinguish between a low dose of the opioid antagonist naloxone (NX) (0.15 mg/70 kg, i.m.; *e.g.,* Drug A) and placebo (*e.g.,* Drug B) under an instructed novel-response drug discrimination procedure in which subjects identify the drug condition as "A", "B", or "N" (neither A nor B - 'novel'). Once the discrimination was acquired, doses of NX alone (0-0.21 mg/70 kg, i.m.), hydromor-phone (HYD) alone (5, 10 mg/70 kg, i.m.) and HYD in combination with NX (0.15 mg/70 kg, i.m.) were rested. Eight of ten subjects acquired the discrimination. Of seven subjects who continued to participate, six maintained the discrimination during testing. NX alone produced dose-related increases in NX-appropriate responding, with some 'novel'-appropriate responding at low doses, and increases in self-reported opioid antagonist adjective ratings. HYD alone produced dose-related increases in 'novel'-appropriate responding, little or no NX-approp-riate responding and increases in self-reported opioid agonist adjective ratings. When combined with NX (0.15 mg/70 kg), HYD produced dose-related decreases in NX-appropriate responding and antagonist adjective ratings and increases in agonist adjective ratings. These results indicate that the behavioral effects of NX are discriminable from placebo and can be altered in a dose-related manner by an opioid agonist under a novel response discrimination procedure, suggesting that this paradigm has utility as a human model of withdrawal.

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BUPRENORPHINE BLOCKADE OF HYDROMORPHONE ACROSS THREE BUPRENORPHINE DOSING SCHEDULES

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Buprenorphine (BUP) dose-dependently blocks the behavioral effects of hydromorphone (HYD) for periods up to 24 hours. The present double-blind study examined the duration of this blockade for up to 96 hours across a 24-, 48- and 72-hour BUP dosing schedule (BDS). Eight, male opioid-dependent outpatients abstinent from illicit opioids and maintained on either 4 or 8 mg/70 kg, s.1. BUP (N=4/group) were exposed to each dosing schedule in a mixed sequence and participated in 10 laboratory sessions. During the 24-, 48- and 72-hour BDS, subjects received their maintenance dose, 2x their maintenance dose or 3x their maintenance dose every 24.48 or 72 hours, respectively. Under the 48- and 72-hour BDS, subjects received placebo on the interposed days. In laboratory sessions, subjects received sequential s.c. injections of saline, 6 and 12 mg/70 kg HYD at 90 minute intervals using a cumulative dosing procedure. As a positive control for HYD effects without BUP blockade, one of these sessions occurred following a three day exposure to 2 mg/70 kg BUP; placebo BUP was not used for ethical reasons. A blood sample was drawn before, and physiology and behavior assessed throughout, each session. As expected, HYD produced the greatest effects under the 2 mg BUP condition. In the 8 mg group, BUP blocked HYD's effects on observer- and subject-rated measures of opioid agonist effects in a dose-related manner for up to 48 hours under the 24-, 48- and 72-hour BDS. BUP blockade of the cumulative 18 mg HYD challenge dissipated by 72 hours. These effects were not replicated in the 4 mg subject group and may reflect differences in BUP metabolism as suggested by plasma BUP levels. BUP did not block physiological responses to HYD in either the 4 or 8 mg group. Overall, the data suggest that the 24- and 48-hour BDS maintain effective blockade of exogenous opioids for up to 48 hours in patients maintained on an 8 mg sublingual BUP dose. However, since blockade may be compromised during the 72-hour BDS, the 72-hour schedule may need to be restricted to patients with appreciable periods of abstinence from street opioids.

OXYCODONE PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONSHIPS IN NORMALS AND PATIENTS

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Preston, *et. al.,* Drug and Alcohol Dependence, 1991; 27:7-17 described the use of a Specific Drug Effect Questionnaire (SDEQ) as part of screening drugs for abuse potential in ex-addict volunteers. The questionnaire consisted of 22 items. A modified version, utilizing 10 items was administered to 74 normal volunteers and 211 pain patients in three bioavailability and five clinical studies which evaluated both immediate-release and controlled-release oxycodone tablets (OxyContin™). The items included 1) Do you feel any effects of the drug? 2) Is your skin itchy? 3) Are you relaxed? 4) Are you sleepy? 5) Are you drunk? 6) Are you nervous? 7) Are you full of energy? 8) Do you need to talk? 9) Are you sick to your stomach? 10) Are you dizzy? Each item was rated on a 100 mm visual analogue scale anchored by "not at a!!" and "an awful lot". For both subjects and patients, the item most significantly related to plasma oxycodone concentration was "feels drug effect". Three of the 8 studies provided correlation coefficients in the range of 0.5 to 0.6. For the testing of opioids in opioid naive volunteers and in patients with pain who are often opioid experienced, the use of a single item from the Modified SDEQ (Do you fee! any effects of the drug?) provides the most predictive PK/PD relationship.

MODULATION OF INTRAVENOUS COCAINE EFFECTS BY CHRONIC ORAL COCAINE IN HUMAN DRUG ABUSERS

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This study is evaluating the direct effects of chronic oral cocaine and its potential modulation of the effects of i.v. cocaine challenges. Inpatient volunteer cocaine abusers (n=5) receive placebo capsules p.o., q.i.d. for 12 days, followed by 25 and 50 mg cocaine p.o., q.i.d. for three to four days each, 100 mg cocaine p.o., q.i.d. for 10 days, and placebo washout for seven days. Cocaine challenges (0, 25, and 50 mg, i.v., one hour apart) are presented during each oral dose and during placebo washout. Daily assessments reveal no adverse effects of chronic oral cocaine on vital signs, quality/duration of sleep, daily mood, or psychomotor performance. Baseline physiological and subjective measurements prior to i.v. cocaine challenge sessions suggest slight oral cocaine-induced increases in heart rate, blood pressure, pupil diameter, and ARCI subscales of stimulant effects (Benzedrine Group and Amphetamine scales), reversible with placebo washout. Challenge session results suggest a decrease in acute cardiovascular and pupil responses (change from baseline) to i.v. cocaine during oral cocaine treatment, sustained for approximately one week following withdrawal of active oral cocaine before reversing later in the placebo washout. There appears to be no change in maximum i.v. cocaine-induced cardiovascular effects following oral cocaine administration and a decrease in both peak scores and change from baseline scores for adjective checklist scores, drug onset analog measures of drug effect, rush, drug liking, good effects, and desire for cocaine, and the ARCI subscales of amphetamine-like effects (Benzedrine Group and Amphetamine scales) and euphoria (Morphine Benzedrine Group scale) in response to i.v. cocaine injections during maintenance on 100 mg oral cocaine q.i.d. A rebound effect was observed following a delay of up to one week after withdrawal of active oral cocaine. These data support the need for further research to evaluate more fully the potential value of agonist substitution approaches to cocaine abuse pharmacotherapy.

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DEVELOPMENT OF A MULTIPLE-CHOICE DRUG DISCRIMINATION INSTRUMENT TO ASSESS BOTH DRUG STRENGTH AND DRUG NOVELTY

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Human drug discrimination paradigms (DD) have been developed over the past ten years and can be used to assess the comparative abuse liability of drugs. Originally designed as simple two-choice experiments, these studies have evolved to include a novel-response option (Bickel *et. al.,* 1993). We are developing a human DD methodology which includes a multiple-choice instrument operating on a two-dimensional analog scale of drug strength (radius) and drug novelty (angle); thus a subject is not forced to classify a continuous percept as one of two or three discrete categories. We are training subjects to use this instrument using a taste discrimination (TD) paradigm. Since the reinforcing properties of food and drug are thought to share a common neurobiological pathway, we hypothesize that TD is a valid method by which to test and train a DD instrument. Subjects (n=14) were trained to discriminate between a sugar solution and distilled water. They were then given various solutions to taste and asked to rate the strength and novelty of each solution compared to the training solutions. Responses were compared to the two-choice and the novel-response alternatives. Preliminary results indicate that this is a sensitive and robust instrument for measuring TD. Future studies may show it to be as sensitive when used in DD studies.

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"CHEATING" IN HUMAN DRUG DISCRIMINATION STUDIES

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An objective of this study was to characterize a methodologic problem in human laboratory studies of the discriminative stimulus effects of orally-administered drugs. Results from a previous drug discrimination experiment revealed that subjects developed strategies to discriminate drug from placebo by tasting the capsule contents. Based on this finding, a study was conducted to evaluate the prevalence of this behavior. Normal subjects (n=30) were recruited for participation in a study involving discrimination of "compounds normally found in foods and beverages". The design and procedures, including monetary reinforcement for correct responses, were similar to many published human drug discrimination studies. Presentation of two substances (lactose and quinine-tainted lactose, contained in identically-appearing capsules) was randomized across sessions and identified only by arbitrary letter code. Subjects displaying statistically significant discrimination behavior within the initial 40 sessions were transferred to a second phase that included thorough oral cavity checks immediately following capsule ingestion. Six of 30 subjects showed significant discrimination during the initial phase. In these six subjects, discrimination behavior was disrupted in the second phase of study by thorough mouth checks. These data suggest that a substantial proportion of subjects will employ strategies that circumvent the experimental objective of discrimination studies which focus on evaluation of CNS mediated drug actions. It is recommended that human drug discrimination studies employ procedures that minimize this potential confound.

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COMPARATIVE ABUSE LIABILITY OF FENTANYL AND REMIFENTANIL

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The abuse liability of remifentanil, a new, short-acting, esterase metabolized phenylpiperidine opioid analgesic, was compared to fentanyl and placebo in a randomized, double-blind, crossover design abuse liability study. Twelve recreational opioid users who were able to reliably detect a test dose of hydromorphone, were enrolled in a nine day study consisting of three different treatment periods (remifentanil, fentanyl, and placebo) randomized into six sequences. Incrementing doses of remifentanil (0.6, 1.2, 1.8, 3.4, 3.0, and 3.6 µg/kg) and fentanyl (0.4, 0.8, 1.3, 2.0, 3.0, and 4.5 µg/kg) were administered IV via an infusion pump: if any dose caused hemoglobin O_2 saturation to drop briefly to 90% higher doses of that drug were bypassed. Subjective measures (Cole/ARC1 scales and VAS items such as "high" and "liking") and physiologic variables (blood pressure, O_2 saturation, and pupil diameter) were measured. Differences from baseline were reduced to an AUC and a peak for each infusion, and each subject's largest response for each of the three drug classes was entered into a 12x3 ANOVA. Almost all active drug vs placebo differences were significant. The maximum fentanyl AUCs were generally significantly larger than the corresponding remifentanil AUCs, but the peaks differed for only a few measures which were not administered quickly enough to capture remifentanil's very brief peak: Cole/ARCI Abuse Potential, Cole/ARCI Stimuation-Motor and Cole/ARCI Unpleasantness-Physical scales. Results were similar for observer rated drug effects. A drug abuser seeking a longer-lasting drug effect might select fentanyl over remifentanil, but these data do not rule out remifentanil abuse when briefer or repeated effects are desired.

DOPAMINE RELEASE MEDIATES CONDITIONED RESPONSES TO COCAINE

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Studies of cocaine-dependent subjects have shown that re-exposure to environmental cues previously associated with cocaine use produces a strong conditioned response characterized by autonomic hyperarousal and increases in subjective measures of cocaine craving. To evaluate the role of dopamine release by such cues, 20 cocaine-dependent inpatients were randomized using a single-dose, crossover, placebo-controlled design to haloperidol (4 mg p.o.) and placebo. Plasma HVA, ACTH, and cortisol were assayed pre- and post-cue exposure. Craving and anxiety were measured pre- and post-cues with visual analogue scales for desire to use cocaine now and for mood changes. Cocaine cues significantly increased anxiety, significantly increased ACTH, cortisol, and HVA. Increases in anxiety and craving resulting from cue exposure were significantly antagonized by pretreatment with haloperidol. Although it has been hypothesized that dopamine depletion may be important to cue-induced cocaine craving this data supports the alternative hypothesis that dopamine release may mediate some of the conditioned responses to cocaine cues.

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FREQUENCY AND ENJOYABILITY OF PLEASANT EVENTS IN COCAINE PATIENTS: COMPARISONS WITH CONTROL GROUPS AND RELATIONSHIP TO TREATMENT OUTCOME

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Behavioral theory posits that drug abuse is associated with non-drug reinforcement deprivation. In laboratory and clinical settings, drug self-administration decreases as non-drug reinforcement increases. Whether drug abusers experience lower reinforcement density than non-abusers in the natural environment is unknown. The present study constitutes an initial step in addressing that question by beginning to characterize "non-drug reinforcement" in cocaine abusers vs. normaIs. The frequency and enjoyability of various "pleasant events" were assessed using the Pleasant Events Schedule (PES) as an approximation of non-drug reinforcement density. The study was conducted in three stages. First. 50 individuals in treatment for cocaine abuse or dependence participated in a pilot study in which they completed the PES and were compared to PES norms. Second, PES data were collected in a more controlled manner from another 50 individuals in treatment for cocaine-dependence as an attempted replication of the initial study. Third, the PES was administered to 50 normal volunteers comparable to the second cocaine sarnple on age, sex, and SES. This provided a more contemporary comparison group than the PES norms, which were collected in 1974. Reliable differences across all three phases of the study included significantly lower overaIl frequency of pleasant activities and lower frequency of non-social, introverted, passive outdoor, and mood-related activities in the cocaine vs. control groups. Cocaine patients generally rated the overall enjoyability of the activities comparable or greater than controls. Results were largely independent of depression and demographic differences between the groups. IV cocaine use, prior cocaine treatment, and polydrug dependence were associated with particularly low frequency of various pleasant activites for cocaine patients. Importantly, greater frequency of non-social activities was a significant yet modest predictor of greater cocaine abstinence in treatment, even when demographics and drug history variables were considered. These results support a behavioral understanding **of** the role of reinforcement deprivation in drug abuse and offer pertinent clinical implications for treating drug abusers.

DRUG ABUSE SYMPTOMS AND ADDICTION SEVERITY: HOW ARE THE SAM AND THE ASI RELATED?

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Two assessment instruments widely used in substance abuse research are the Addiction Severity Index (ASI) and the WHO/NIH Composite International Diagnostic Interview-Substance Abuse Module (SAM). The ASI measures the severity of problems in seven life areas and the SAM obtains DSM and ICD abuse and dependence diagnoses for alcohol and 11 categories of drugs. Data are from a NIDA study on the reliability and validity of substance use disorders in which 332 subjects from both community and treatment settings were interviewed with both instruments. The analyses indicate that higher ASI scores generally correspond with one or more abuse/dependence criteria compared with no criteria symptoms (SAM) for the four most commonly used substances (alcohol, marijuana, cocaine, and opiates). The number of DSM-IV criteria met in the SAM were significantly correlated with composite scores in most areas measured by the ASI; the exceptions primarily involve the ASI medical section. Overall, there are few gender differences in the relationship between ASI scores and the presence of one or more DSM-IV criteria (SAM); Because the two instruments complement each other, using both is recommended to provide a comprehensive assessment of both diagnostic category and severity across multiple dimensions.

DEVELOPING GENDER AND CULTURALLY-SENSITIVE ASSESSMENT INSTRUMENTS

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The Addiction Severity Index and other assessment instruments commonly used for clinical and research purposes do not adequately address the needs and problems of women. If unmet, needs in these areas may limit potential for recovery in treatment. For an evaluation study of drug treatment programs for women in the criminal justice system, a range of womenís issues were identified and incorporated in a gender- and culturally-sensitive interview. This poster critiques the ASI, highlighting the ways in which it fails to capture the behaviors and everyday realities of drug-using women involved in crime. Issues unrecognized by the ASI include violence against women, HIV/AIDS, parenting responsibilities, homelessness, ethnically and racially-specific beliefs, gender roles and expectations, and the social context of drug use among women in urban poverty. The poster focuses on violence against women, HIV/AIDS, and women's drug use. These issues are discussed and examples garnered from ethnographic observations and interviews are included. Selected items from the research interview illustrate strategies for assessments that more accurately reflect cultural and gender issues relevant to the study population. Recommendations are made for modifying other assessment instruments to more appropriately address womenís issues.

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GENDER COMPARISON OF SELF-REPORTED DRUG EFFECTS

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Questionnaires describing subjective drug effects are widely used in drug abuse research and have been validated almost exclusively with males. Public health concerns and federal regulations require that women participate in clinical research studies. This study compared me responses of male (n = 28) and female (n = 30) opioid maintenance patients on a standard subjective effects battery. Subjects described their past subjective experiences of opiate intoxication, cocaine intoxication, sedative intoxication, and opiate withdrawal; no drugs were administered. The four test conditions were presented randomly and consisted of two phases each. Subjects first gave an open-ended verbal description of their physical and subjective experiences. These were tape-recorded, transcribed, and the frequency of specific responses analyzed. Subjects also completed a battery of questionnaires including the Addiction Research Center Inventory (ARCI) Short Form, the Weak Opiate Withdrawal Scale (WOW), and visual analog and adjective rating scales. The verbal reports and questionnaire results showed distinct patterns for each drug condition, and the qualitative profiles for both were consistent with those obtained in acute drug administration studies. There were no significant differences between males and females on the ARCI, WOW or visual analog scales, and gender differences were observed on only 5 of 71 adjective rating scales. Significant gender differences were found for 19 of 104 (18%) of spontaneously reported drug effects. There was high concordance between the specific drug effects described by subjects and those items included on the structured checklist; only 12 items that appeared on the adjective checklist were not spontaneously mentioned during the interview phase. These results suggest that this subjective effects battery is sensitive in a contemporary population and that responses to these instruments are similar in males and females.

GENDER DIFFERENCES IN MOOD AND SCID-III-R DIAGNOSES IN COCAINE-DEPENDENT PATIENTS

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Patients (N=97) who met the DSM-III-R criteria for lifetime and current cocaine dependence (95%) or abuse (5%) were evaluated for DSM-III-R Axis I diagnoses by SCID-P and Hamilton Depression Rating Scale (HDRS). Other lifetime and current dependence: alcohol (34%). Lifetime dependence currently in remission: cannabis (28%), hallucinogens (14%), alcohol (13%). Lifetime organic disorders: delusional (52%), hallucinosis (39%), mood disorder-depressed type (28%). Current organic disorders: delusional (37%). mood disorder-depressed type (27%), hallucinosis (22%). The gender ratio of patients and SCID diagnoses were similar (1:4). Our patients (N=97) had minor depressive ratings based on the HDRS. First ratings of patients (n=62) with two ratings, showed a trend towards females scoring higher on HDRS ratings than males (9.77 and 6.24, $p<0.10$). During the first two weeks of hospitalization. there was a decrease in HDRS scores which was similar to that reported by Griffin, *et. al.,* (1989).

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MCMI-II AXIS II PROFILES AND SCID-P AXIS I DIAGNOSES OF COCAINE DEPENDENT RESEARCH PARTICIPANTS

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Patients (N=113) who met the DSM-III-R criteria for lifetime and current cocaine dependence (95%) or abuse (5%) were evaluated for DSM-III-R Axis I diagnoses by SCID-P and Axis II diagnoses by Millon Clinical Multiaxial Inventory-II (MCMI-II). Other lifetime and current dependence: alcohol (29%). Lifetime dependence currently in remission: cannabis (26%). hallucinogens (14%). and alcohol (12%). Lifetime organic disorders: delusional (35%), hallucinosis (30%), mood disorder-depressed type (25%). Current organic disorders: delusional (14%), mood disorder-depressed type (14%), hallucinosis (12%). MCMI-II (n=68) Clinical Personality Patterns: antisocial (59%), narcissistic (51%), passive-aggressive (47%), and aggressive-sadistic (40%), and Severe Personality Disorders: borderline (16%) and paranoid (9%). Our methods and findings were similar to Craig and Olson (1990).

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SENSITIVITY OF THREE MMPI-2 ADDICTION SCALES: THE APS, AAS, AND MAC-R IN A METHADONE CLIENT POPULATION

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This study examined the sensitivity of three MMPI-2 addiction scales in methadone maintenance clients: the Addiction Potential Scale (APS), Addiction Acknowledgement Scale (AAS), and the MacAndrew Alcoholism Scale-Revised (MAC-R). One hundred two unemployed methadone client volunteers (55 men, 47 women) completed the MMPI-2 as part of the intake package for a vocational problem-solving research protocol.

Even at the less-stringent cutoff score of T ≥ 60 the APS performed poorly with these subjects, identifying only 22% of men and 52% of women. Significant differences by ethnicity and gender were noted: the APS was more likely to identify White men (11 of 27; 41%) than Black men (0 of 18, $p < .001$) and Latino men (1 of 9; 13%, $p < .003$). Similarly, the APS identified more White women (8 of 19; 42%) than Black women (5 of 24; 21%); this difference was not significant ($p = .185$). Two Latina women were not included in the analyses. but neither was identified by the APS. At the more stringent cutoff of T≥ 65, only 17% of men and 17% of women were identified. The poor performance of the APS with these subjects is puzzling and somewhat troublesome, particularly given the low hit rate overall and the ethnic and gender differentials.

By contrast, at T ≥ 60 the AAS identified 89% of men and 96% of women; there were no significant ethnic or gender differences. Using a cutoff of raw score≥ 24, the MAC-R identified 87% of men and 72% of women, with no significant ethnic or gender differences. Using a cutoff of raw score ≥ 22 for the women resulted in a hit rate of 94%. Sensitivity of these two scales declined using the more stringent cutoffs of T ≥ 65 for the AAS and raw ≥ 28 for the MAC-R: at these cutoffs the AAS idendfied 69% of men and 87% of women; the MAC-R identified 48% of men and 34% of women. Additional research clearly is necessary.

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COMPARATIVE USE OF THE ADDICTION SEVERITY INDEX IN FRENCH AND NORTH AMERICAN HEROIN USERS: COMPARISON OF HEROIN USERS SEEKING TREATMENT IN BORDEAUX AND PHILADELPHIA

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The goal of this study was to determine whether opioid dependent subjects seeking treatment in Philadelphia and Bordeaux, France could be assessed with the same instrument. Used worldwide, the Addiction Severity Index is 45 minutes semi-structured interview that provides assessment of problem severity in seven functional areas in which substance abusers are commonly impaired. A group of 30 French opioid dependent (DSM III-R) subjects seeking treatment were compared to a similar group of 25 Philadelphia opioid dependent subjects. Both ASI interviewers were trained in Philadelphia.

	Bordeaux	Philadelphia
age (y)	32	36
female subjects	33%	28%
ASI composite score Medical	.26	.16
ASI composite score Employment	.57	.65
ASI composite score Alcohol	.14	.09
ASI composite score Drug	.35	.31
ASI composite score Legal	.19	.17
ASI composite score Family/Social	.21	.21
ASI composite score Psychological	.44	.22

Our results indicate that heroin users from different cultural environments, assessed with the ASI, have similar profiles.

ABUSE-NEGLECT REPORTS BY DRUG-INVOLVED ADOLESCENTS

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Previous reports suggest that child abuse and neglect (CAN) may contribute to the development of Substance Use Disorder (SUD). We present an interview (Colorado Adolescent Rearing Interview; CARI) for studies of CAN among adolescents with SUD, examining whether they will describe CAN experiences if forewarned that clinicians report such experiences to child protection agencies. We examine differences between male and female patients, the use of drugs by perpetrator and victim, and the relationship of CAN and SUD. Subjects were 110 male patients, 57 female patients, and 15 community comparison males. Among patients 72% of girls and 45% of boys gave responses almost certainly indicating CAN; only one (7%) of the comparison males did so. About 40% of both perpetrators and victims were "nearly always" or "sometimes" intoxicated during CAN. Victims perceived that alcohol-drug use was among the most common sequelae of CAN. We found modest but significant correlations between CARI scores on the one hand and symptoms of Substance Dependence, Conduct Disorder, and Major Depression on the other. However, in a multiple logistic regression controlling for depression, gender, and other relevant measures the CARI score was not severity after analyses controlled for depression, ADHD, and Conduct Disorder symptoms. Reports of CAN are very prevalent in adolescents with SUD and Conduct Disorder. Even if CAN is not a significant contributor to SUD, identifying it is crucial for protection of patients and other children.

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DIFFERENTIAL EFFECTS OF DRUGS ON ETHANOL-INDUCED EXCITATION OR DEPRESSION IN MICE

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It has been suggested that increases in locomotor activity induced by drugs of abuse may involve mechanisms related to reinforcement. To assess if ethanol-induced hyperactivity in mice provides a sensitive baseline, several drugs were tested in combination with ethanol on locomotion and loss of righting reflex. Diazepam reduced ethanol-induced excitation, probably by potentiating the sedative effect of ethanol. Flumazenil and Ro 15-4513 did not affect ethanol's actions. Ethanol is known to potentiate GABA function, however, from these results the role of GABA in ethanol-induced excitation remains unclear. In agreement with observations that ethanol and NMDA antagonists show some similarities in pharmacological properties, dizocilpine (MK 801) shifted the ethanol dose response curve to the left, indicating a potentiation of the effects of ethanol. d-Amphetamine increased ethanol excitation at doses which themselves increased locomotion and haloperidol decreased the stimulant effect of ethanol and increased its sedative effect. These results do not provide much help in clarifying the role of dopaminergic mechanisms in the effects of ethanol. As observed with diazepam and haloperidol, the calcium channel blocker, nifedipine, reduced ethanol excitation and increased ethanol sedation. Ethanol-induced hyperactivity in mice is useful to screen drugs that potentiate the stimulant effect of ethanol but other models such as ethanol-induced loss of righting reflex are needed to differentiate a blockade of the stimulant effect of ethanol from a potentiation of its depressant effect.

REDUCTION OF ALCOHOL INTAKE IN ALCOHOL PREFERRING FAWN-HOODED AND P RATS BY NORIBOGAINE, THE PRIMARY METABOLITE OF IBOGAINE

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Recently, we reported that Ibogaine when is given IP or orally, but not SC, significantly and dose-dependently suppressed alcohol intake in three different strains of alcohol preferring rats (Rezvani *et. al.,* 1995). Thus, it was hypothesized that an active metabolite of Ibogaine may play an important role in its suppressing effect on alcohol intake. To test this hypothesis, the effects of a newly-identified Ibogaine metabolite, Noribogaine (12 Hydroxyibogamine) (Hearn *et. al.,* 1995) on alcohol intake was determined. Alcohol drinking Fawn-Hooded (n=15) and P (n=20) rats were injected with vehicle, or 5, 10, 20, or 30 mg/kg Noribogaine and food, waler, and alcohol intakes were measured at 2, 4, 6, and 24 hours after the injection. These data show that Noribogaine significantly and dose-dependently decreased alcohol intake in both strains. Although the higher dose of 30 mg/kg also reduced food intake, the magnitude of suppressing effect of this dose on alcohol intake was greater than that on food intake. In both strains of rats water intake tended to be elevated. These results confirm our previous findings and suggest that Ibogaine metabolites may be potentially useful in the treatment of alcoholism. It is speculated mat Noribogaine exerts its attenuating effects on alcohol intake by increasing the level of serotonin in the brain.

DRUG EFFECTS ON A MULTIPLE SCHEDULE OF ETHANOL AND SACCHARIN RESPONDING

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Animal studies using either home-cage drinking or, more recently, simple schedules of operant responding have shown that many drugs can alter rates of ethanol self-administration. In many of these studies, the selectivity of EtOH-maintained responding for drug effects was not determined. For the present study, we developed a multiple schedule of EtOH and saccharin self-administration in rats using 2-lever operant chambers. Over successive 60 minute sessions, FR-4 responding for .05 ml deliveries of water and, later, increasing concentrations of EtOH was engendered in Long-Evans rats using both partial water restriction and pre-session feeding. After the rats were reliably responding during each five minute component on alternating levers for a 10% (w/v) EtOH solution, the water-deprivation and then the pre-session feeding were gradually discontinued. Substitution of water for EtOH deliveries in one component resulted in a rapid extinction of waler responding with no effect on responding during the EtOH component, indicating that EtOH was serving as a reinforcer. Introduction of 0.1% saccharin/water solution into one delivery system resulted in responding for both the 10% EtOH and saccharin/water solutions during alternating components. Daily, repeated, pre-session i.p. injections of EtOH resulted in a dose-dependent and selective attenuation of EtOH responding without affecting saccharin responding. Repeated pre-session injections of phencyclidine nonselectively suppressed both ethanol and saccharin self-administration. At this time, other drugs with EtOH-like effects, such as GABA agonists are being tested for their ability to selectively attenuate EtOH self-administration.

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EFFECTS OF ABUSED 'INHALANTS ON MULTIPLE SCHEDULE PERFORMANCE IN MICE

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It has been hypothesized that the abused inhalants share both the excitatory and depressant effects observed with acute ethanol and barbiturate administration. Previous investigations in our laboratory have shown that solvents concentration-dependently decrease high baseline rates of responding (FR) while producing biphasic effects under schedules of intermediate responding (FI & DRL). In an attempt to further delineate the effects of inhalant exposure, eight SWISS mice were trained to lever press under a multiple FR 20-FI 3' schedule of milk reinforcement. Concentration differences and magnitude of effect were determined for 30-minute exposures of toluene (100-6,000 ppm), 1,1,1-trichloroethane (TCE; 1,000-14,000 ppm), and methoxyflurane (100-6,000 ppm). Cumulative and temporal session data demonstrated that lower to middle concentrations of toluene, TCE and methoxyflurane had little to no effect on FR and FI responding while higher concentrations significantly decreased responding in both components. Generally, methoxyflurane was more potent than toluene with toluene being more potent than TCE in reducing FR and FI response rates. This study demonstrates that toluene, TCE and methoxyflurane produce qualitatively similar results on FR and FI responding but response rate increasing effects were not readily evident under a multiple schedule.

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NALTREXONE EFFECTS ON ORAL ETHANOL-REINFORCED RESPONDING IN RHESUS MONKEYS

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Twelve rhesus monkeys were given opportunities to respond concurrently either lo obtain ethanol or water; most of the monkeys had histories of exposure to opioids (*e.g.,* etonitazene) or phencyclidine-like drugs. Eight of the twelve reliably self-administered ethanol relative to water over a three hour period. Ethanol concentration [0.25 - 32 gm/L] was altered; increases in concentration produced a bitonic preference in reinforced responding and increases in ethanol intake. Individual differences in ethanol intake were considerable, and were representative of individual differences of other studies of oral ethanol intake in rhesus monkeys. Naltrexone (0.032 - 0.32 mg/kg i.m.) reduced both ethanol and water responding across monkeys, and, in some cases, reduced ethanol-reinforced responding more than water responding. Naltrexone was studied at a range of ethanol concentrations that produced different intakes. This type of study may be appropriate to begin to examine parallels to the studies in humans in which naltrexone decreases certain ethanol-related behaviors.

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ALPHA-INTERFERON PREVENTS THE EFFECT OF ETHANOL WITHDRAWAL ON OPIOID SYSTEMS IN RATS

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The effect of recombinant a-interferon (α-IFN) (10,000 U, i.p.) on the binding characteristics of μ- and δ-opioid receptors and content ß-endorphin and met-enkephalin in rats under chronic ethanol administration (10 months, 15% solution of ethanol) was studied. Scatchard analysis revealed that chronic ethanol administration and especially ethanol withdrawal (24 h) reduced the high affinity binding sites for ^{3}H-naloxone andlow affinity binding sites for ^{3}H-D-ala-2, D-leu-5-enkephalin. Effect of ethanol was abolished by α-IFN injection during two weeks only after alcohol withdrawal. The concentration of ß-endorphin and met-enkephalin in the tissue and blood plasma of these animals was simultaneously determined. Alcohol withdrawal after chronic ethanol administration was shown to significantly decrease the level of ß-endorphin in anterior pituitary and blood plasma, the level of met-enkephalin was reduced in striatum, adrenal cortex and plasma. Alpha-interferon prevented the development of ethanol-induced changed for ß-endorphin - in tissue and plasma; for met-enkephalin - in adrenal cortex and plasma, but its level in striatum became even lower. Thus, after alcohol withdrawal the administration of α -IFN led to the normalisalion of altered parametrs of opioid response.

EVALUATION OF THE REINFORCING EFFICACY OF ORALLY-DELIVERED PCP AND ETHANOL: VARIED FEEDING CONDITIONS

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The purpose of this study was to evaluate the effects of feeding conditions on oral PCP and ethanol self-administration by using a behavioral economic analysis (*e.g.,* demand functions -- consumption as a function of unit price) and by break point on progressiveratio (PR) schedules. Six rhesus monkeys were trained to orally self-administer PCP (0.25 mg/ml) or ethanol (8% wt/vol) and water under concurrent fixed ratio (FR) schedules during daily 180-min drug sessions. Each subject was given concurrent access to either PCP or ethanol and water during each session while the FR schedules for both available liquids were changed in a nonsystematic fashion (FR 4-128). Results indicated that food satiation decreased PCP consumption by approximately 45% at all FRs except 128 (73% decrease). Ratio related decreases in ethanol deliveries (from 44.9% to 87.9%) were observed as FR increased from 4 to 128. Concurrent PR schedules were also used with PCP or ethanol and concurrent water (PR steps = 8, 16, 32, 64, 128, 178, 256, 356, 512...4096). A range of PCP (0.06 - 1.0 mg/ml) and ethanol (2% - 32%) concentrations were tested under food deprivation and satiation conditions. Break point varied with concentration. In these studies P-max (estimate of unit price or FR at which maximal responding occurred) and break point decreased during food satiation for both PCP and ethanol indicating that food satiation reduced the maximal response output for drug. The results suggest that food satiation decreases the reinforcing efficacy of drug self-administration. Higher drug prices also enhance the suppressant effects of food satiation.

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CUMULATIVE EFFECTS OF ALCOHOL ON HUMAN BEHAVIOR

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The immediate and next-day effects of cumulative doses of alcohol on task performance and verbal reports of drug effects were investigated in a residential study. Twelve adult moderate alcohol users, blind to the study drug, gave written consent and participated four days per week over four consecutive weeks. Daily schedules included a 6.5-hour work period beginning at 9:30 a.m. and an eight hour social-access period beginning at 5:00 p.m.. At the start of every hour during the social-access period, beginning at 6:00 p.m., as well as at 8:30 a.m. the following morning, subjects completed behavioral assessments, including digit-symbol substitution, repeated acquisition, and number recall tasks, and visual-analog ratings of drug effect. Five identical doses (0, 0.22 or 0.44 g/l) were administered once per hour, beginning at 6 p.m., immediately after assessments were completed. Each active dose condition was administered once per week; 48-hours separated successive active drug days. Cumulative dose-related changes in digit-symbol substitution, repeated-acquisition and number-recall performance, and increases in verbal reports of 'High, 'Sedated,' 'Potency,' and 'Liking,' were observed during evening assessments, but no residual effects were observed on assessment performance the following morning. Next-day performance during the work period was also minimally affected when active doses were administered the previous evening. In summary, behavioral assessments, which were sensitive to the acute effects of alcohol, effectively indicated the absence of residual alcohol effects on next-day work performance.

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INTRAVENOUS ETHANOL FOR THE MAINTENANCE OR DETOXIFICATION OF THE CRITICALLY ILL ALCOHOLIC

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A chart review was undertaken at UMMS in order to answer four research questions: 1) Is the current hospital practice of initiating, continuing, and terminating IV ethanol consistent with literature recommendations? 2) Are undetectable blood alcohol levels sufficient to prevent delirium tremens? 3) Is IV ethanol effective in detoxifying alcoholics? 4) What percentage of patients who receive IV ethanol is seen by the University of Maryland alcohol consult team? Sixty-eight critically ill alcoholics who received intravenous ethanol therapy were selected for the study. A single reviewer retrieved patient demographics, clinical course, and outcome data. Using "SPSS for Windows", statistical analysis was completed. Fifty-six (76.5%) patients were admitted for alcohol related reasons, such as trauma secondary to intoxication or alcoholic organ dysfunction. Yet, only 26 (38%) had any documented risk factors for delirium tremens. In many of these patients, the basis for ethanol administration was either totally absent or completely undocumented. Seventeen (26%) were started on oral ethanol after the intravenous was discontinued. No clear criteria were used to determine who should receive oral therapy. Patient withdrawal decreased with the passing of time suggesting an improvement in clinical condition either due to ethanol therapy or simply to extended abstinence. Twelve (17.6%) patients were discharged from the hospital on the same day their ethanol therapy was discontinued, placing them at risk for acute alcohol withdrawal. Only seven (10%) received any sort of alcohol treatment referral on discharge. In conclusion, the guidelines for initiating, continuing, and discontinuing IV ethanol were either unclear or not systematically followed. Also, the high number of patients with alcohol-related admission diagnosis along with the low number of alcohol consults and discharge referrals suggests a need for educating staff on the treatment of alcoholism. Finally, a controlled clinical trial of ethanol vs an alternative therapy in the trauma population should be carried out.

TIME-LIMITED INTERPERSONAL GROUP PSYCHOTHERAPY WITH ALCOHOLICS - A PILOT PROJECT

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Traditional treatment programs for substance abusing patients have focused primarily on biologically, socially and behaviourally directed treatment strategies, often omitting psychological approaches. The contemporary literature shows increased interest in psychotherapeutic treatments with a strong move towards group formats. A time-limited group therapy was conceived and piloted with a group of eight alcohol dependent patients who had achieved sobriety and for whom there was a clinical indication for a psychotherapeutic intervention to assist in relapse prevention. An interpersonal paradigm was elaborated collaboratively with the patient as a central treatment issue. The focus contained elements of current interpersonal concern which repetitively arose in relationships and which could be a precipitating or perpetuating factor in drinking behaviour. Group sessions were held weekly for 1 3/4 hours for 20 weeks. Patients were asked to complete an interpersonal inventory and symptom checklist. These were completed again at the end of treatment as well as a retrospective drinking profile and review of other concurrent treatment. The data suggests that alcohol dependent patients are able to make important interpersonal gains in a time-limited group therapy without having an adverse effect on drinking behavior.

ETHNIC AND GENDER FACTORS IN ADDICTION RESEARCH

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Alcoholism is one of the major problems confronting the African American community. The literature indicates that there is an increase of alcohol abuse among women. Overall, there exist limited data addressing alcoholism and the African American female. Smith 1981, reports that African American women have different drinking patterns from that of White women. There is increasing motivation among researchers to understand ethnicity and gender factors in order to provide adequate solutions to the substance abuse problem. Federally funded research now mandates a study designed with ethnic and gender representation appropriate to the goals and objectives of the proposed project. This study's primary objective was to examine values, beliefs, family patterns, and cultural factors that may influence the use of alcohol among this population. In addition, we examined the forces that may dissuade the participation of African American females in substance abuse treatment and addiction research. A sample size of 200 African American women were surveyed. Participants were enrolled in psychology courses attending a historically black university is Southeast Texas. Measures included a 50 item questionnaire developed by the researchers and the four item "CAGE" instrument. Findings identified 12% of the sample as problem drinkers.

NEUROCHEMICAL CHARACTERIZATION OF A NEW CLASS OF NOVEL NICOTINIC RECEPTOR ANTAGONIST

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We hypothesize that the nicotinic receptor subtype which modulates dopamine (DA) release in striatum is different from the nicotinic receptor subtype which binds [^{3}H]nicotine. A series of N-substituted nicotine analogues were synthesized and evaluated for inhibition of nicotine-evoked [^{3}H]DA release from rat striatal slices and for displacement of [^{3}H]nicotine binding from rat striatal membranes. The effects of the analogues were compared to the classical nicotinic antagonist, DHBE. The order of potency in the release assay was S-N-octylnicotinium iodide (NONI) > DBHE > S-N-allylnicotinium iodide (NANI). The IC50 for NONI was - 30% that of DHBE. Also, NONI was the most efficacious compound, completely inhibiting nicotine's effect. Moreover, the Ki's for DHBE, NANI and NONI displacement of [^{3}H]nicotine binding were 0.06 ± .01, 2.38 ± 0.24 and 20.1 ± 1.6 μM, respectively. Thus, the lack of correlation between inhibition of nicotine-evoked [^{3}H]DA release and displacement of [^{3}H]nicotine binding exhibited by these nicotinic antagonists supports the suggestion that different nicotinic receptor subtypes are responsible for modulation of DA release and nicotine binding to brain membranes.

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EPIBATIDINE: RECONSIDERATION OF THE NICOTINE RECEPTOR PHARMACOPHORE

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Nicotine receptor ligands may represent an untapped target for the development of novel therapeutic agents. Nicotine itself produces undesirable side effects; however, these side effects may be eliminated by design of agents with greater selectivity. The availability of a reliable pharmacophore model would aid the design process. Although a ten year old model is available, it was formulated on the basis of a limited number of ligands that were known at the time. We have synthesized and evaluated > 30 new analogs for purpose of investigating structure-affinity relationships (SAFIR), QSAR, and pharmacophore development. One study investigated the bulk that can be tolerated by nicotine receptors. For example, epibatidine is a new, high-affinity nicotine receptor ligand with considerable bulk. Because both optical isomers bind with similar affinity (Ki = 0.05 nM) and with higher affinity than (-)nicotine (Ki ca 2 nM), it seems reasonable that a volume composed of the overlap of the two isomers (198 A^3) is readily accomodated by the receptor. Although this volume is larger than that of (-)nicotine (155 A^3). overlap of all three (SYBYL 6.la; Multifit) reveals that (-) nicotine overhangs the epibatidine volume by 19 A^3. It might be argued that the difference is due primarily to lack of an N-methyl group on epibatidine, however, using a combined methyl-epibatidine overlap, the overhang is still 12 A^3. Thus, despite its overall smaller volume, nicotine may bind with lower affinity than epibatidine because of its occupation of a receptor region not occupied by the larger agent. Studies such as these will allow us to better define the binding region of nicotine receptors with respect to its molecular dimensions and structural requirements.

NICOTINE AS A CONDITIONAL STIMULUS FOR ROTATION: CONTEXT IS CRITICAL

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Rats were lesioned unilaterally by microinjection of 6-hydroxydopamine aimed at substantia nigra. They subsequently were administered 0.05 mg/kg apomorphine (s.c.) and 0.4 mg/kg nicotine (i.p.) contemporaneously on each of six consecutive days. This treatment resulted in rotation (circling) directed away from the lesioned side which increased significantly upon repeated treatment. Weeks after the series of paired drug administrations, injection of nicotine alone, but not of saline alone, resulted in rapid contralateral rotation. The conditioned rotation was highly context dependent. Rats that had been administered the paired drug treatments in their home cages circled in response to nicotine administered in their home cages, but not when nicotine was administered in hemispherical test chambers. Rats that had been administered the paired treatments in the hemispherical test chambers circled in response to nicotine alone in that environment, but did not circle in response to nicotine administered in their home cages. The results show that nicotine can serve as a conditional stimulus for circling when administered in one context, but not in another, in the same organism.

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EVIDENCE FOR THE INVOLVEMENT OF PHOSPHOLIPASE A2 MECHANISMS IN THE DEVELOPMENT OF STIMULANT SENSITIZATION

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Evidence suggests that phospholipase A2 (PLA2) activation is involved in mediating LTP. Considering the pharmacological similarities between LTP and stimulant sensitization, it seems possible that PLA2 activity might also have a role in the induction of stimulant sensitization. In this study we have investigated whether PLA2 inhibition, using quinacrine, has any effects on stimulant induced behavioral sensitization. Both locomotor and stereotypic behavioral sensitization were dose dependently blocked in rats pretreated with quinacrine (8-2.5 mg/kg, i.p.) 15 minutes prior to cocaine (30 mg/kg, i.p.), when tested 72 hours after treatment with cocaine (15 mg/kg, i.p). Similar results were also found with amphetamine (2 mg/kg, i.p.) sensitization using a ten day treatment regimen with testing on day 11. Quinacrine alone did not modify the acute effects of cocaine or amphetamine induced locomotion and stereotypy. The ability of PLA2 stimulation, using melittin, to sensitize animals to the effects of cocaine was also tested. Local injections of melittin (0.1 μg/0.4 μl) into the ventral tegmental area (VTA) sensitized the subsequent stimulation of locomotor activity, stereotypy and nucleus accumbens dopamine release by cocaine. when tested 72 hours later. Local injections of melittin (0.1-1.0μg/0.6 μl) into the nulceus accumbens had a moderate sensitizing effect on locomotion. Finally, quinacrine (16 mg/kg) pretreatment 45 minutes before melittin injection (0.1 μg) (final 30 minutes under stereotaxic anesthesia) signilicantly induced the ability of mellittin injections in the VTA to sensitize the locomotor and stereotypy response to cocaine. These results indicate that PLA2 activation may play a role in the induction of stimulant sensitization. It is proposed that that PLA2 activity in mesolimbic dopamine neurons, at the level of the cell bodies and perhaps the nerve terminals, is involved in the biochemical mechanisms mediating the development of stimulant sensitization.

EFFECT OF TRAINING DOSE ON NICOTINE DISCRIMINATION IN SMOKERS

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Nicotine may have different subjective effects at low vs. high doses (*e.g.,* "stimulating" vs. "sedating"). We examined the effect of training dose on behavioral discrimination across a range of nicotine doses. Male and female smokers (n=24) randomly assigned to low (10 ug/kg) vs. high (30 ug/kg) nicotine training dose groups were trained to discriminate this dose from placebo on Day 1 (≥80% correct). On Day 2, both groups received 0, 5, 10, 20, and 30 ug/kg in ascending order (30 minutes between dosings) and were tested for generalization with their training dose using a behavioral discrimination task. Subjective responses were also assessed. On Day 2, nicotine-appropriate responding was significantly greater in low vs. high dose groups, especially at 5 ug/kg. This effect of training dose was observed primarily in women and not men. Furthermore, responding was less sharply dose-dependent in women vs. men, suggesting reduced sensitivity of discrimination across doses in women. Discrimination was strongly associated with the subjective effect of "head rush", and to a lesser degree with decline in "urge to smoke" and "jittery". These results indicate the importance of training conditions in influencing behavioral discrimination of nicotine as well as subjective responses. They also suggest that, under certain conditions, women may be less sensitive than men to manipulations of nicotine dose.

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NICOTINE EFFECTS ON HUMAN BRAIN ACTIVITY AS ASSESSED BY FUNCTIONAL MRI

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Nicotine produces a wide variety of physiological and behavioral effects in man including increases in cognition, attention and motor activity together with the development of tolerance and dependence. Since the neuroanatomical localization of nicotine's behavioral actions are not well understood, we have employed functional magnetic resonance imaging (fMRI) to non-invasive determine nicotine's functional anatomy in the human CNS. Subjects were nine experienced cigarette smokers between the ages of 19 and 31 (smoking years averaged 6.7). Nicotine doses of 0.75, 1.5 and 2.25 mg were administered IV over a period of 20-30 seconds. Heart rate, EKG and arterial blood pressure were monitored as were subjective responses of high, rush, liking and anxiety. Experiments were performed using a GE 1.5 Tesla Signa MR scanner equipped with specialized gradient and RF coils for whole brain imaging, a gradient echo EPI pulse sequence and an inplane resolution of 3.75 mm. Changes in MR signal amplitude were determined based upon the working hypothesis that parenchymal derived signal should follow a pharmacokinetic mode1 accounting for the onset and duration of nicotine action. Pixels passing threshold were superimposed upon SPGR anatomic images, warped into stereotaxic space and averaged across subjects to produce projection maps. A dose-dependent regional activation was seen in discrete cortical areas including frontal lobes (Brodmann areas 6,8,9,44,45) cingulate gyrus (BA 23,24,32), posterior parietal lobe (BA 7), temporal lobe (BA 22,37), insular, thalamus and putamen. Saline was ineffective in altering fMRI activation. Peak drug effects were observed between 2.5-7 minutes after drug injection with a half-life of less than 15 minutes. The observed activation areas are consistent with the behavioral profile of nicotine's effects.

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EFFECTS- OF A NICOTINE PATCH ON ENDOCRINE MEASURES OF TOBACCO WITHDRAWAL

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Tobacco smoking may increase plasma levels of adrenocorticotropin (ACTH) and cortisol, however, the effects of tobacco cessation on endocrine measures has not been as thoroughly studied. Plasma cortisol, ACTH and prolactin (PRL) were measured in ten residential volunteers who underwent four seven day cycles of ad lib smoking (Friday to Monday) and no smoking (Tuesday to Thursday). On nonsmoking days combinations of three placebo and 10 mg transdermal nicotine patches were applied for doses of: 0, 10, 20, and 30 mg. Dose conditions were held constant for the three day nonsmoking periods. Blood was collected at 1 p.m. on Monday to Thursday. In the 0 mg condition (abstinence) plasma levels of PRL, ACTH and cortisol increased (115- 140% baseline) on Tuesday and Wednesday. The increases were not statistically significant. All doses of the nicotine patch reduced the PRL increase but there were no consistent or dose related effects on ACTH or cortisol levels. Decreases in heart rate, increases in nicotine withdrawal scores and performance impairment occurred during nicotine abstinence. There was no correlation between those measures of severity of tobacco abstinence and changes in ACTH, cortisol or PRL. These results indicate that there are minimal endocrine changes associated with short-term tobacco withdrawal and provide little support for the use of ACTH in treatment of nicotine withdrawal.

CIGARETTE SMOKING AND OTHER SUBSTANCES OF ABUSE

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We examined the relationships among primary drugs of abuse and studied participants' responses to questions about the relationship of cigarette smoking and their other drug use. Eighty-eight substance-abusing subjects enrolled in a study comparing two forms of advice to quit smoking identified their primary drug of abuse as either heroin (N=25), crack/cocaine (N=29), or alcohol (N=34). No differences were found in terms of average age, educational level, marital, employment or legal status, Heroin abusing subjects tended to have more stable housing. Cocaine abusing (including crack) subjects were more likely to be African American. At baseline, there were no differences in numbers of cigarettes smoked or in CO levels. In response to a series of questions, crack/cocaine subjects were less likely to have a cigarette after using cocaine ($p<.05$) and were less likely to smoke cigarettes while using cocaine ($p<.05$). Heroin abusing subjects were more likely to smoke the same amount whether or not they were using heroin ($p<.05$). Heroin abusers smoked less if in withdrawal than crack/cocaine abusers, who would smoke less than alcohol abusers ($p<.05$). Alcohol abusers were more likely to think about quitting smoking cigarettes when not using alcohol than were abusers of crack/cocaine or heroin when not using their primary drugs ($p<.05$). However, at the one month follow-up interview (N=60), only the findings for heroin abusing cigarette smokers replicated. Crack/cocaine subjects did tend to report fewer number of cigarettes on the average at one month when compared with those in the heroin and alcohol groups. Taking into consideration the baseline observations, the data from this study suggests that smoking cessation programs must take into consideration any concomitant drug or alcohol use when devising interventions.

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CIGARETTE SMOKING IN WOMEN AND GENDER RELATED STRESS

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Cigarette smoking in women may be related to the pressure to be thin. This longitudinal field study followed 54 late adolescent and young adult females (mean age=18.5 years) for eight months. Stressors, peronality variables, and substance usage were measured at the beginning of the study (T1), after five months (T2), and after eight months (T3). Pearson product-moment correlations at T1 showed relationships between cigarette smoking and family income level (r=.225; p=.049), prevalence of family members and close friends who smoke (r=.511; p=.000), current alcohol usage (r=.286; p=.003), and stress concerning physical appearance (r=.222; p=.O35). These correlations were used to construct a theoretical model predicting variance in cigarette smoking between T1 and T3. Although no significant correlations were found for hostility or self-confidence, they were retained in the predictive model on theoretical grounds. Multiple regression analyses, controlling for cigarette smoking at T1, with cigarette smoking at T3 as dependent variable, were employed to refine this model. Hypothesized predictor variables were treated as co-independent variables. Initial results showed that none of the hypothesized variables had an independent effect. Subsequent analyses showed that interactions between the hypothesized variables did predict variance in cigarette smoking. The final model contained two main effects:1) cigarette smoking at T1 (Beta=.592; p=.000), and,2) an interactive variable containing prevalence of family members and friends who smoke, current alcohol usage, self-confidence, hostility, and stress concerning physical appearance (Beta=.358; p=.001). This model had high predictive value (Multiple R=.904; Multiple R-SQ=.817; F-ratio=107.422; p-v,alue=.OOO). These data support research suggesting that cigarette smoking in young women is affected by me prevalence of family and friends who smoke, alcohol usage, self-confidence, and hostility. It also suggests that stress concerning physical appearance may contribute to cigarette smoking.

IMPACT OF MOOD ON WEIGHT GAIN AFTER QUITTING SMOKING

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Weight gain with smoking cessation is well-documented. Given the frequent occurrence of weight gain with depression, it is possible that the degree of weight gain associated with smoking cessation might be mediated by mood factors. The present study was undertaken to explore the impact of mood state on weight gain during and after the quitting process. Data of 350 subjects enrolled in two smoking cessation trials were analyzed; primary analyses assessing the relation of affective factors to weight gain were conducted on abstinent subjects only. In accord with previous findings, weight gain was predicted by abstinence status. History of depression, gender, and change in mood from pre- to post-cessation assessments were used to develop a model predicting weight gain in subjects who were abstinent from cigarettes at the end of smoking-cessation treatment (N = 201) and at one-year follow-up (N = 87). With the exception of depression history positive men, a consistent sex difference in the impact of mood factors on weight gain emerged. At post-treatment, women with a history of depression gained more than those without whereas men with a history of depression gained less than those without. At one year follow-up, weight gain was predicted by improved mood in nondepressive men and by worsened mood in all women.

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REFERENCES: Available from first author upon request.

ATTRITION FROM SMOKING CESSATION STUDY IN SUBSTANCE ABUSERS

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This work reports on the analysis of attrition data from an on-going smoking cessation study conducted with substance abusers. A two-group randomized design was used to assign subjects to standard advice to stop smoking or a more intensive advice session linked to health consequences from smoking. We hypothesized that a larger proportion of subjects who did not attend the advice session or who dropped out by the six month follow-up would be: 1) in the linked-advise group, 2) reporting more significant life events, and 3) less motivated to quit smoking at baseline. Of the 89 subjects who have been in the study long enough to complete the six month follow-up, 70 (79%) have completed the advice session; 49 (55%) have completed the six month follow-up. We compared attrition before the advice session and follow-up attrition on: group assignment, significant life events, drug use in the last 30 days, number of reported quit attempts al intake, enjoyment from smoking reported at baseline, and demographics. The only attrition differences found were related to current drug use and reported enjoyment from smoking at baseline. Subjects who reported cocaine use in the past 30 days were more likely to drop out of the study before six months (61.5% vs. 39.1%, chi-square=3.46, $p<.063$). Subjects reporting higher enjoyment from smoking had both higher attrition before advice ($p<.028$) and by the six month follow-up ($p<.043$).

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TOLERANCE TO THE RESPIRATORY-STIMULANT EFFECTS OF CAFFEINE IN RHESUS MONKEYS

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The respiratory effects of caffeine were characterized in three utuanesthetized, seated rhesus monkeys while ventilation was measured continuously with a pressure-displacement plethysmographic technique. Caffeine administration (i.m.) increased respiratory frequency (f) and minute volume (V_E) during exposure to air alone (normocapnia) or 3%, 4% and 5% CO_2 balanced in air (hypercapnia). After chronic administration of 10 mg/kg caffeine for eight consecutive days, increases in f were far less pronounced, and V_E did not differ statistically from non-drug, baseline conditions. A higher dose of caffeine (30 mg/kg) produced marked increases in f and V_E, but the effects were comparable to those obtained with 10 mg/kg in non-tolerant subjects. When chronic administration was terminated and the acute effects of caffeine were redetermined, sensitivity returned to levels obtained prior to chronic administration within nine days. Hence, tolerance to the respiratory effects of caffeine was rapid, surmountable and reversible. In a separate group of six monkeys, chronic administration of 10 mg/kg caffeine for ten consecutive days had no significant effect on caffeine pharmacokinetics as determined by peak plasma levels and plasma half-life. This study establishes a nonhuman primate model to investigate underlying biochemical mechanisms involved in caffeine tolerance.

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TOPOGRAPHIC QUANTITATIVE EEG RESPONSE TO ACUTE CAFFEINE WITHDRAWAL

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Thirteen normal Ss using ≥300 mg of caffeine daily received quantitative EEGs before and during four days of verified caffeine abstinence. Significant alpha and theta absolute Power increases occurred over frontal cortex during the four days of withdrawal for several, but not all, Ss. Group analyses (repeated measures ANOVAs) across baseline and withdrawal conditions confirmed that alpha and delta absolute power significantly increase over frontal cortex during caffeine withdrawal. Absolute power of theta activity significantly increased with caffeine abstinence at all scalp electrodes except 02 and OZ. Beta absolute Power remained unchanged. Alpha frequency (Hz) significantly decreased at all scalp electrodes during abstinence. No frequency changes were seen in the theta, delta, and beta bands. Repeated measures ANOVAs applied to interhemispheric coherence measures revealed that alpha and theta coherence significantly increased over frontal cortex throughout the first two days of abstinence while theta and delta coherence decreased significantly over posterior cortex during the abstinence period. For some Ss caffeine was reinstituted following four days of abstinence. Alterations in the variables discussed above returned to baseline levels within 15 minutes of coffee intake. Paired t-tests contrasting EEG indices after caffeine reintroduction with baseline measures were uniformly nonsignificant.

CAFFEINE REINFORCEMENT: THE ROLE OF WITHDRAWAL

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The purpose of this study was to determine if caffeine is consumed by moderate users mainly for its positive reinforcing effects (presumably correlated with mild stimulant effects) or mainly for its negative reinforcing effects (*e.g.,* to prevent or alleviate withdrawal symptoms). Subjects (n = 16) had a daily caffeine consumption of 200 - 500 mg and they participated in three outpatient sessions. Beginning at 10:00 pm the night before each session, subjects were required to follow dietary restrictions eliminating all sources of caffeine which lasted until the session was completed approximately 19 hours later (≈ 5 pm). During the first two sessions, subjects received either placebo or caffeine (each subject's average daily intake) in random order, double-blind. When the subjects returned in the late afternoon, they completed the Profile of Mood States (POMS), a caffeine withdrawal questionnaire, and a Multiple Choice Form on which subjects made a series of discrete choices between receiving the drug again or receiving varying amounts of money. This form also included negative amounts of money to assess how much subjects would forfeit from their pay to avoid aversive effects (*e.g.,* withdrawal symptoms after placebo). During the third session, one of the subject's previous choices on the Multiple Choice Forms was randomly selected and the consequence of that choice was implemented. This helped to ensure that subjects would complete the forms carefully. Placebo administration significantly increased self-reported feelings of "worn out," "drowsy/sleepy," "headache," and "flu-like feelings" relative to their average daily caffeine dose. On the Multiple Choice Forms, subjects chose to receive caffeine rather than an average of $0.66. In contrast, subjects chose to forfeit an average of $3.03 from their pay to avoid receiving placebo again. These results indicate that in moderate caffeine consumers (≈ 2 - 5 cups of coffee) caffeine functions predominately as a negative reinforcer which prevents or alleviates withdrawal symptoms.

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CAFFEINE ABSTINENCE: A RESIDENTIAL LABORATORY STUDY

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The effects of caffeine withdrawal were examined in a residential laboratory, where caffeine intake could be carefully controlled, and a range of behaviors measured within and across days. Twelve subjects (10M, 2F), who reported consuming caffeine daily (min. 200 mg/day), participated in a 17-day residential study. Experimental days approximated a typical work day. Subjects worked on five computer tasks assessing memory, vigilance, and psychomotor skills, from 1000-1700, with a one hour break for lunch; visual analog, subjective-effects measures were completed ten times/day. From 1700-2330, subjects engaged in private or social recreational activities. A variety of caffeine-free foods, including snacks, meals, and beverages were available. Subjects were maintained on caffeine (100 mg tid: 0945, 1345, 1745), except on days 5-6 and 12-13, when caffeine was replaced by placebo. Substituting placebo for caffeine, *i.e.* abstinence, resulted in increased ratings of "Headache" and "Sleepy," and decreased ratings of "Energetic." Subjects also spent less time talking and more time engaged in private activities during caffeine abstinence. Performance measures were not significantly affected by the caffeine manipulation. Caffeine administration following abstinence was associated with increased ratings of "Motivated" and "Self-confident," and decreased ratings of "Tired." Caffeine re-administration also decreased total caloric intake by reducing the number of meals. These results indicate that (1) abstinence from caffeine selectively influenced subjective effects without altering performance on tasks assessing memory, vigilance or psychomotor skills, and (2) caffeine's slimulant effects on food intake, social behavior, and subjective measures were enhanced following two days of caffeine abstinence.

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A SURVEY OF CAFFEINE CESSATION

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Whether caffeine should be viewed as a drug of dependence is debatable, in part due to the lack of systematic data on how many caffeine users try to stop caffeine use, how often they try to do this, or why they wish to stop. We examined these questions as part of a telephone interview about caffeinated beverage and nicotine use among 196 randomly selected adults. Ninety-six percent of Ss had ever used and 83% presently use one or more caffeinated beverages on a weekly basis. Twenty percent of everusers of coffee, 34% of everusers of tea, and 33% of everusers of soda had stopped using that particular beverage; however, only 14% had stopped all caffeinated beverages. In comparison, 60% of eversmokers had quit smoking. The most common reasons for caffeine and nicotine cessation were health concerns (85% for each). Worry of addiction was a less common reason (19% for caffeine and 33% for nicotine). Among current caffeine users, 11% had tried to stop all caffeinated beverage use in the past year, while 42% of current smokers had tried to quit smoking. On a scale of 1 = not at all to 10 = extremely difficult, current caffeine users rated the anticipated difficulty in stopping all caffeine use permanently as 4.2 and current smokers rated the difficulty of stopping smoking permanently as 8.2. On a 10-pt scale, current users rated the severity of the addiction to caffeine as 3.9 and 7.9 for nicotine. Further studies are needed on the prevalence, reasons and success of caffeine cessation attempts and characteristics of those who stop caffeine use.

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CLINICIAN VALIDATION OF ALGORITHM-BASED CAFFEINE AND NICOTINE DEPENDENCE

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Eight clinicians rated the presence and degree of drug dependence in 35 written case reports depicting caffeine, nicotine, or alcohol use and problems. The reports were derived from a structured interview for DSM-III-R criteria for drug dependence taken during a random-digit-dial telephone survey. The reports were rated with drug blinded and with drug identified. The results reported below were similar across these two groups. Test-retest reliability based on 22 cases was .91, .95, and .95 across the three drugs. Rater concordance with algorithm-defined existence of dependence was 97% for caffeine, 100% for nicotine, and 89% for alcohol. Raters often made a diagnosis of dependence when the algorithm did not when the drug was caffeine or nicotine but not when the drug was alcohol. In summary, clinicians agreed with algorithm-derived diagnoses of caffeine and nicotine dependence.

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PERSISTENT CHANGES IN OPEN FIELD BEHAVIOR FOLLOWING METHAMPHETAMINE NEUROTOXICITY IN RATS

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Repeated administration methamphemmine (METH) leads to well-documented, long-term decreases in brain serotonin and dopamine. However, despite dramatic reductions in these neurotransmitters, very few baseline changes in behavior have been observed following neurotoxic regimens of METH. The present study was undertaken to further examine behavioral and neurochemical consequences of METH neurotoxicity. Adult, male Sprague-Dawley rats received injections of saline or METH (6.5 mg/kg s.c.) four times daily for four days. Ten days following treatment, behavior was assessed in a large (4 ft x 4 ft) plexiglass open field apparatus. Four days following behavioral assessment, animals were sacrificed and the brains examined for changes in serotonergic function. METH-treated animals showed significant increases in locomotor activity and rearing relative to saline controls. The increases in behavior occurred despite the fact that animals had been drug-free for ten days. Paroxetine binding revealed significant reductions in serotonin reuptake sites in several brain regions, including neocortex, hippocampus and dorsal raphe in METH-treated animals. The results suggest that METH neurotoxicity produces significant behavioral changes, which may be due to decreases in serotonergic and/or dopaminergic function. The results may have implications regarding the use of neurotoxic amphetamines in humans.

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DRAMATIC. FACILITATION OF METHAMPHETAMINE TOXICITY BY MELATONIN

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Large doses of methamphetamine (METH) are toxic to some CNS serotonergic neurons and cause a long-term decline in associated neurochemical parameters such as tryptophan hydroxylase (TPH: the rate-limiting enzyme for serotonin synthesis), and tissue content of serotonin (5HT) and its principal metabolite, 5-hydroxyindoleacetic acid (5HIAA). Although the mechanism of METH's neurotoxicity remains to be elucidated, it has been suggested that this drug causes the production of reactive free radicals that damage serotonergic neurons. To test this hypothesis, we coadministered the naturally occurring antioxidant, melatonin, with multiple high doses of METH. According to the free radical theory, the presence of melatonin should antagonize METH-induced cytotoxicity. Surprisingly, the presence of melatonin not only did not reduce the serotonergic effects of METH, but dramatically enhanced the METH-induced decline in striatal TPH activity and 5HT and 5H1AA content. Melatonin similarly increased a METH-induced decline in hippocampal and cortical serotonergic neurochemical parameters. The mechanism for the facilitation of METH toxicity by melatonin is currently being investigated.

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EFFICACY-RELATED DIFFERENCES IN BEHAVIORAL EFFECTS OF DOPAMINE D1 AND D2 AGONISTS

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Dopamine agonists differing in efficacy may have qualitatively differing behavioral effects in monkeys. To further evaluate possible efficacy-dependent differences, the effects of D1 and D2 high-efficacy agonists (dihydrexidine, (+)-PHNO, respectively), partial agonists (SKF 77434, SDZ 208-911) and antagonists (SCH 23390, remoxipride) were studied in squirrel monkeys trained to discriminate injections of methamphetamine from saline. Both the D1 agonist dihydrexidine and the D2 agonist (+)-PHNO generally substituted for methamphetamine. Similar to the effects of D1 and D2 receptor antagonists, the D1 partial agonist SKF 77434 and the D2 partial agonist SDZ 208-911 generally did not substitute for methamphetamine, but surmountably antagonized the discriminative stimulus effects of methamphetamine. The results indicate that the interoceptive effects of methamphetamine can be reproduced by agonists which selectively stimulate either D1 or D2 receptors. Furthermore, in monkeys, the behavioral effects of D1 and D2 partial agonists are comparable to those of D1 and D2 receptor blockers but dissimilar to those of full D1 and D2 agonists, suggesting that dopamine partial agonists might be developed as therapeutic agents to counteract the subjective effects of methamphetamine.

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EFFECTS OF METHAMPHETAMINE AND PHENCYCLIDINE ON RESPONDING UNDER CONCURRENT SCHEDULES BY PIGEONS

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Pigeons were trained to respond under concurrent (conc) variable-interval (VI) schedules of food presentation, after which the effects of drugs were determined. Under conc VI 30 VI 300, conc VI 60 VI 240, and conc VI 60 VI 60 second schedules, the pigeons distributed their responses on the two keys as predicted by the matching law (88.3%, 75.9%, and 51.5% on the preferred key, respectively). Intramuscular injections of methamphetamine increased the percentage of responses on the preferred key under all schedules except conc VI 240 VI 60 and decreased key switching under all of the concurrent schedules. The decreases in switching occurred at lower dose levels than the increases in responding on the preferred key. Phencyclidine (PCP) increased the percentage of responses on the preferred key and decreased key switching under the conc VI 30 VI 300, but its effects on the percentage of responses on the preferred key were variable under the other concurrent schedules. Increases in responding on the preferred key after PCP were accompanied by decreases in key switching. Methamphetamine and PCP interfere with the ability of pigeons to discriminate reinforcement frequency under concurrent schedules by increasing time spent responding on the preferred key and decreasing key switching.

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MORPHINE, MDMA, MDA AND NEXUS PRODUCE A CONDITIONED PLACE PREFERENCE IN NEWLY HATCHED CHICKENS

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The current study was undertaken to evaluate the feasibility of using newly hatched chickens in the conditioned place preference procedure. Groups of one day old chickens were initially confined to each side of a place preference apparatus containing a mirrored divider for five minutes per side. After initial exposure to each side of the apparatus, the divider was then removed and individual chickens were placed in the center of the apparatus for five minutes and tested for a preference for either side. To prevent distress vocalization caused by isolation, the divider was placed along one wall of the apparatus such that half the mirror was in one side and half in the other. During the next three days, each chicken received an i.p. water injection in the preferred side, followed by an i.p. injection of drug in the non-preferred side. Exposure time was ten minutes per side. The day following the final water-drug exposures, individual chickens were again tested for a place preference. A drug was considered to have produced a place preference if significantly less time was spent in the previously preferred side and significantly more time was spent in the previously non-preferred side. Morphine, MDMA (3,4-methylenedioxymethamphetamine), MDA (3,4-methylenedioxyarnphetamine), and Nexus (4-bromo-2,5-dimethoxyphenethylamine) all produced a place preference, but there were differences in the effects of these drugs. For example, morphine produced a place preference at 1 but not 1.5 or 2.5 mg/kg, although at the higher doses chickens did spend less time in the previously preferred side. The inability to produce a preference at the higher doses may have been due to the fact that these doses tended to put the chickens to sleep. MDMA and Nexus produced a place preference at intermediate (1, 2 and 4 mg/kg for MDMA and 1 and 2 mg/kg for Nexus) but not at lower or higher doses, while MDA only produced a preference at the higher (4 and 8 mg/kg) doses. These results suggest that the newly hatched chicken may be a convenient species for studying drug-induced place preferences.

PHARMACOKINETICS OF METHAMPHETAMINE IN EXTENSIVE (EMs) AND POOR METABOLIZERS (PMs)

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Methamphetamine (MAMP) is a central nervous system stimulant metabolized to 4-OH-MAMP by cytochrome P4502D6 (CYP2D6) a genetically polymorphic enzyme, absent in 7% of Caucasians (PMs). Plasma and urinary kinetics of MAMP and their metabolites after oral administration in EMs and PMs under alkaline and normal urine conditions were studied in 12 healthy subjects (8 EMs and 4 PMs). On two separate occasions they received a single oral dose of 10 mg of MAMP HCl after random oral administration of $NaHCO_3$ 1.8 gr or placebo QID. Plasma and urine samples were collected for 24 and 48 hours respectively. MAMP and its metabolites were analyzed by GC-NPD. One compartment pharmacokinetic model fit the data best. MAMP was well absorbed in all subjects. For extensive metabolizers, mean plasma peak levels of p-OH-methamphetamine (main metabolite) were 6.37 ± 0.85 ng/ml (range: 5 to 7.2 q/ml) under alkaline urine condition and 5.73 ± 0.84 ng/ml (range: 4.2 to 6.8 ng/ml) under normal urine condition, while for poor metabolizers, mean plasma levels of p-OH-MAMP were 2.67 ± 0.73 ng/ml (range: 2 to 3.8 ng/ml) under alkaline urine condition and 2.58 ± 0.76 ng/ml (range: 2 to 3.8 ng/ml) under normal urine condition. PMs showed significantly decreased conversion to 4-OH-MAMP ($p < 0.001$) compared to EMs subjects. These data show differences in pharmacokinetics of MAMP metabolism in EMs and PMs.

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REPEATED AMPHETAMINE INDUCES SENSITIZATION BUT NOT CONDITIONED PLACE PREFERENCE IN *FYN* MUTANT MICE

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The introduction of null mutations ("knockouts") into individual genes is a powerful tool in elucidating single gene effects on complex physiological and behavioral processes. Mice with a mutation in the nonreceptor tyrosine kinase gene *fyn* are significantly impaired in their development of long-term potentiation (LTP) and spatial learning. Because the neuroadaptive response to repeated stimulant treatment shares several common features with LTP, we hypothesized that *fyn* mutant mice may be deficient in the development of behavioral sensitization and conditioned place preference (CPP), a process known to require spatial learning. No differences in baseline locomotion or in the acute locomotor response to 3 mg/kg d-amphetamine were observed between *fyn* mutant and wild-type (C57BL/6J-129/SV hybrid) mice. The locomotor response to amphetamine was significantly augmented in both *fyn* mutant and wild-type mice following eight daily injections ($p < 0.005$), with no differences between strains. Similarly, no difference in the development of cocaine-kindled (45 mg/kg daily) seizures was observed between *fyn* mutant and wild-type mice. In contrast, when given a choice between two chambers previously paired with saline or amphetamine, only wild-type mice preferred the drug-paired chamber ($p < 0.01$). Whether the lack of CPP in *fyn* mutant mice reflects blunted amphetamine reinforcement or impaired association of spatial cues with the drug cue remains unclear. Targeting of *fyn* and other signal transduction genes may be a powerful strategy in the study of cellular and behavioral actions of abused drugs.

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ROLE OF CENTRAL α_2-RECEPTORS IN MEDIATING THE SYMPATHOINHIBITORY RESPONSE ELICITED BY AMPHETAMINE

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Studies in this and other laboratories have shown that cocaine and amphetamine (AMPH) decrease sympathetic nerve discharge (SND) in anesthetized rats. Bilateral microinjection of the α_2-adrenergic antagonist idazoxan (IDA) into the rostraI ventrolateral medulla (RVLM) decreases the sympathoinhibitory (SI) response to cocaine. The purpose of this study was to determine whether α_2-adrenergic receptors in the RVLM also mediate the SI response elicited by AMPH. Pentobarbital-anesthetized, mechanically-ventilated male Sprague-Dawley rats (275-300 g) were studied. Renal SND was recorded (0.03-3 kHz) using bipolar platinum electrodes. Pressor responses (>30 mmHg) and increases in SND elicited by the microinjection of l-glutamate (50 nl of 500 mM) were used to locate RVLM. IDA (3 nMol in 50 nl; n = 7) or saline (0.9% in 50 nl; n = 7) were then bilaterally microinjected into RVLM and live minutes later AMPH (0.5 mg/kg) was administered iv. Resting MAP and HR were not significantly different between the saline- and IDA-treated groups. Injection of saline or idazoxan did not alter MAP, HR or SND. In saline-treated rats, AMPH produced large (-50 ± 10%) and prolonged (66 ± 10 min) decreases in SND. Microinjection of IDA significantly reduced the duration (to 19 ± 4 min), but not the magnitude (-49 ± 8%) of the SI response to AMPH. The pressor responses elicited by AMPH in the saline- and IDA-treated groups (25 ± 4 and 33 ± 4 mmHg, respectively) were not significantly different, nor were the HR responses different (-3 ± 27 and 25 ± 21 bpm, respectively). We conclude that the SI response elicited by AMPH involves, at least in part, an α_2-adrenergic mechanism in RVLM.

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FEEDBACK ON TASK PERFORMANCE AFFECTS AMPHETAMINE SELF-ADMINISTRATION BY HUMANS

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The interaction between feedback on task performance and drug choice was evaluated in eight subjects living in a residential laboratory. On sample days, subjects received placebo or amphetamine prior to a work session and were told three hours later, at the end of the session, that their task performance was either “better” or “worse” than average. If subjects received a “better” feedback message, they earned $55 and if they received a “worse” message, they earned $15. On other days, subjects chose between amphetamine and placebo under conditions in which performance feedback was present or absent. Feedback on choice days was always consistent with feedback received on sample days and was not based on actual performance. Although subjects predominantly chose amphetamine under no feedback conditions, amphetamine choice significantly decreased when they were given “worse,” compared to “better,” feedback messages. These results demonstrate that amphetamine served as a reinforcer under conditions in which drug self-administration did not influence monetary earnings. However, amphetamine self-administration decreased when subjects were told that amphetamine impaired their performance on work tasks, resulting in reduced earnings. Thus, an important variable that has implications for workplace performance is whether drug-taking will affect the delivery of another reinforcer (*i.e.,* money).

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PMMA AS A DISCRIMINATIVE STIMULUS

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Phenylisopropylamine (PIA) Drugs of abuse can be divided into hallucinogens (*e.g.,* DOM), stimulants (*e.g.,* amphetamine), and designer drugs. The latter group contains agents with hallucinogen and/or stimulant character, and may also contain mechanistically unique agents such as MDMA. PMMA or paramethoxy-methamphetamine is a new designer drug that lacks quantifiable hallucinogenic and stimulant character (Pharmacol. Biochem. Behav. 1988, 31, 9) but that produces MDMA-like stimulus effects in rats (Pharmacol. Biochem. Behav. 1992, 43, 759). In order to further investigate this agent, we trained a group of S-D rats to discriminate 1.25 mg/kg of (±)PMMA (ED50 = 0.44 mg/kg) from saline vehicle in a two-lever operant procedure using a VI-15s schedule of reinforcement. PMMA-stimulus generalization failed to occur with DOM or S(+)amphetamine; however, generalization occurred with (+)MDMA and S(+)MDMA (ED50 = 1.32 and 0.48 mg/kg). Administration of R(-)MDMA resulted in partial (68%) generalization. S(+)PMMA (ED50 = 0.32 mg/kg) seems to be primarily responsible for the stimulus effects of the racemate; R(-)PMMA produced only partial generalization at 1.75 mg/kg. Being pharmacology similar, structurally related, yet simpler in structure, than MDMA, PMMA may constitute the parent of this class of PIA designer drugs.

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THE NEUROCHEMICAL EFFECTS OF METHCATHINONE ON MONOAMINE SYSTEMS

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Methcathinone ("CAT") is a designer amphetamine-like drug which is a synthetic derivative of cathinone prepared from ephedrine. Its first reported use as a drug of abuse in the U.S. came in the early 1990's in Michigan, however it has been a popular drug of abuse in the former Soviet Union for several years. Users claim methcathinone is more desirable than cocaine or methamphetamine. Relatively little data exist on the mechanism of action of methcathinone; however, it has been reported to be toxic to brain dopamine (DA) and serotonin (5-HT) neurons (Martello *et. al.,* Soc. for Neurosci, # 419.15, 1994). We assessed the monoamine response to methcathinone treatment by monitoring the striatal activity of tyrosine hydroxylase (TH) and tryptophan hydroxyhse (TPH), the rate-limiting enzymes in the synthesis of DA and 5-HT, respectively. Rats were given four doses of methcathinone (30 mg/kg) four hours apart, and sacrificed 18 hours or seven days after the last dose. Another group of rats received one dose of methcathinone (30 mg/kg) and was sacrificed two hours later. TPH activity was significantly decreased in the 18 hour and IWO hour groups (28% and 35 % of control, respectively). TH activity was significantly decreased only in the 18 hour group (48% of control) and did not appear significantly different at seven days. Our findings demonstrate that methcathinone treatment can profoundly alter monoamine systems in the striatum.

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5-HT-MEDIATED ENDOCRINE AND BEHAVIORAL RESPONSES IN RATS TREATED WITH HIGH DOSES OF FENFLURAMINE

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High doses of fenfluramine (FEN) are known to cause degeneration of serotonin (5-HT) nerve terminals, but physiological correlates of this putative toxicity have not been well characterized. We examined endocrine and behavioral responses to acute FEN challenge in rats that had been previously treated with repeated high dose FEN. Male Sprague-Dawley rats (N=32) were anesthetized with metofane and fitted with indwelling jugular catheters. After a seven day recovery period, FEN (20 mg/kg, s.c.. bid) or saline (1 ml/kg, sc) was administered for four consecutive days. At one and two weeks after the final chronic treatment, rats were challenged with FEN (1.5 mg/kg, iv) or saline (1 ml/kg, iv). Repeated blood samples (0.5 ml) were withdrawn immediately before and at 15, 30 and 60 minutes after iv injection. Plasma was assayed for corticosterone and prolactin by double-antibody radioimmunoassay. Various behaviors including locomotor activity, flat body posture, forepaw treading and penile licking were scored in the same subjects. The corticosterone response to acute FEN challenge was significantly blunted in FEN-treated rats at one and two weeks postchronic treatment. In contrast, prior FEN exposure had no effect on prolactin responses elicited by FEN. FEN-induced locomotor activity and flat body posture were abolished in FEN-treated rats, but other behaviors were similar regardless of pretreatment. Our data suggest that anatomical and biochemical indicators of FEN neurotoxicity are accompanied by functional deficits in specific populations of 5-HT neurons. However, other populations of the 5-HT neurons exhibit mechanism(s) of compensatory neuroadaptation since not all 5-HT-mediated responses are affected by prior FEN exposure. Alterations in responsiveness to FEN in the present study could be operationally defined as FEN tolerance and may not necessarily be indicative of true neurotoxicity.

δ-ANTISENSE OLIGO REVEALS THE LOSS OF δ ANALGESIA INDUCED BY COLD WATER SWIMMING IN THE MOUSE

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The antinociception by cold water swimming (CWS; 4 °C, 3 min) was blocked by intrathecal (i.t.) administered NTB (10 mg) or NTI (5 mg), but not BNTX (1 mg), CTOP (50 ng) or norBN1 (5 mg) in mice, indicating that it is mediated by the activation of d-opioid receptors (DOR) in the spinal cord. CWS-induced antinociception in mice, like that induced by i.t. administered [D-Ala^2]deltorphin II (Delt; 5 mg), was prevented by i.t. pretreatment with DOR antisense oligo (AS oligo; 163 pmol) once a day for three days, but not for one day. The effects of the activation of spinal DOR 24 hr earlier on the antinociception induced by i.t. treated Delt or CWS were studied in mice pretreated i.t. with DOR AS oligo once a day for one day. Groups of mice were pretreated i.t. with DOR AS oligo, mismatch oligo (MM oligo; 163 pmol) or saline 10 min before DOR activation. The activation of spinal DOR were performed by i.t. treatment with Delt or CWS. Twenty-four hours after the activation of spinal DOR. mice were treated i.t. with Delt or submitted to CWS, and tail flick response was measured ten or seven minutes after i.t. treated Delt or CWS, respectively. Mice treated i.t. with saline or submitted to warm water swimming (24 °C, 3 min) served as a control for the activation of DOR. The activation of DOR by i.t. treated Delt or CWS did not have any effect on i.t. treated Delt- or CWS-induced antinociception in mice pretreated with saline or MM oligo. However, i.t. treated Delt- or CWS-induced antinociception were signiticantly attenuated in mice pretreated with DOR AS oligo by activation of DOR with i.t. treated Delt or CWS. The results indicate that CWS, like i.t. treated Delt, activates spinal DOR and enhances the down-regulation of DOR function which is revealed by the inhibition of the DOR synthesis with DOR AS oligo.

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THE δ-ANTISENSE OLIGO PREVENTS THE RECOVERY FROM ACUTE ANTINOCICEPTIVE TOLERANCE TO δ AGONISTS IN MICE

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An intrathecal (i.t.) injection of [D-Ala^2]deltorphin (DT), a opioid receptor (DOR) agonist, produced an acute antinociceptive tolerance to a subsequent i.t. challenge of DT which lasted three to nine hours and recovered in 12 to 24 hours. The experiments were designed to examine the effect of an antisense oligodeoxynucleotide (AS oligo) to DOR mRNA on the recovery from antinociceptive tolerance to DOR agonists in male ICR mice. Groups of mice were injected i.t. with DT (6.4 nmol) alone or a combination of DT or other opioid agonists and DOR AS oligo or mismatch (MM) oligo. Mice were then challenged i.t. with DT (6.4 nmol) at different times after DOR AS oligo injection and the tail-flick response was measured 10 minutes later. I.t. pretreatment with DOR AS oligo (1.63 to 163 pmol), but not MM oligo (163 pmol), dose-dependently prevented the recovery from tolerance to DT. I.t. injection of DAMGO (19.5 pmol), a μ-receptor (MOR) agonist, or U50,488H (107 nmol), a κ-receptor (KOR) agonist, also produced tolerance to a subsequent challenge of DAMGO or U50,488H. However, treatment of DOR AS oligo (163 pmol) did not prevent the recovery from tolerance to DAMGO or U50,488H, indicating that the inhibition of DOR protein synthesis by i.t. injection of DOR AS oligo selectively blocks the recovery from acute antinociceprive tolerance to i.t. administered DOR agonist, but not MOR or KOR agonist. In the DOR binding experiments, mice were scarified 24 hours after the treatment with i.t. DT (6.4 nmol) and DOR AS oligo (163 pmol). Suspensions of the crude synaptic membrane of the mouse spinal cord were incubated with [^{3}H]DSLET, a selective DOR agonist ligand, for two hours at 25 ºC. I.t. concomitant administration of DT with DOR AS oligo greatly decreased me [^{3}H]DSLET bindings as compared to i.t. saline or DT alone. We therefore propose that a single stimulation of DOR by DT induces a long lasting change of DOR which is sensitive to DOR agonist. The recovery from DOR-mediated antinociceptive tolerance does not depend on immediate reversal of DOR, but rather on the replenishment by newly synthesized DOR protein.

ANTINOCICEPTIVE EFFECTS OF SELECTIVE NONPEPTIDIC δ-OPIOID RECEPTOR AGONIST, TAN-67, IN DIABETIC MICE

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The antinociceptive effects of 2-methyl-4aa-(3-hydroxyphenyl)-1,2,3,4,4a,5,12,12aa-octahydro-quinolino[2, 3, 3, -g] isoquinoline (TAN-67), a nonpeptidic d-opioid agonist, Male ICR mice were rendered diabetic by an injection of streptozotocin (200 mg/kg. i.v.). The antinociceptive potencies were examined using the acetic acid abdominal constriction test and me tail-flick test in non-diabetic and diabetic mice, TAN-67 produced a marked and dose-dependent inhibition of the number of acetic acid-induced abdominal constrictions in both non-diabetic and diabetic mice. The antinociceptive effect of TAN-67 in the acetic acid abdominal constriction test in diabetic mice was greater than that in non-diabetic mice. The ED_{50} (95% confidence limits) of TAN-67 in diabetic mice (6.0 [3.5 - 10.5] mg/kg) was significantly lower than that in non-diabetic mice (31.4 [14.2 - 69.4] mg/kg). The antinociceptive effect of TAN-67 was not antagonized by pretreatment with either ß-funaltrexamine, a selective μ-opioid antagonist, or nor-binaltorphimine, a selective k-opioid antagonist. When BNTX (0.3 mg/kg, s.c.), a selective d_1-opioid antagonist, was administered ten minutes before treatment with TAN-67, the antinociceptive effect of TAN-67 was significantly reduced. However, naltriben, a selective d_2-opioid antagonist, has no effect on the anitnociceptive effect of TAN-67. Furthermore, in the tail-flick test, TAN-67 at doses of 3 to 30 mg/kg, s.c., produced a dose-dependent antinociceptive effect in diabetic, but not in non-diabetic mice. These results suggest that TAN-67 produced an antinociceptive effect through the activation of d_1-opioid receptors in both non-diabetic and diabetic mice.

KETAMINE AND FELBAMATE ATTENUATE TOLERANCE TO MORPHINE ANALGESIA

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Ketamine (Ket) and felbamate (Fel) are clinically available drugs that have NMDA receptor antagonist activity. Recent studies have demonstrated that competitive (LY274614) and noncompetitive (MK801 and dextromethorphan) NMDA receptor antagonists attenuate or reverse morphine (MOR) tolerance (Inturrisi, Reg. Pept. 54: 129-130, 1994). To determine whether Ket or Fel modulate tolerance, they were administered 15 or 30 min prior to each dose of morphine or saline. The tolerance paradigm utilizes increasing doses of MOR (sc, tid at 10, 20 and 40 mg/kg per day). The MOR tail-flick ED50 in CD-1 mice on day four increased from 4.3 mg/kg to 23.1 mg/kg. The MOR ED50 values for Ket at 10, 3 and 0.3 mg/kg sc were 5.8, 11.7 and 19.4 mg/kg, respectively, demonstrating a dose dependent attenuation of tolerance. Fel at 300 mg/kg ip attenuated tolerance (ED50 = 7.3 mg/kg) while the 100 mg/kg dosage was ineffective (ED50 = 19.3 mg/kg). These doses of Ket or Fel, alone, do not alter morphine ED50 values. These results suggest that ketamine and felbamate may be of value in reducing or preventing tolerance to morphine's analgesic effects.

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L-TYPE CALCIUM CHANNEL MODULATION IN MOUSE SPINAL CORD, BRAINSTEM, AND STRIATUM IN ACUTE AND CHRONIC MORPHINE EXPOSURE

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A rise in neuronal intracellular calcium levels has been shown to occur concomitantly with morphine tolerance, although the mechanism of calcium elevation and its role in tolerance development are unknown. Tolerant animals, compared to placebo-treated controls, showed a four-fold shift to the right in the dose-response curve for Bay K 8644's antinociceptive effects when administered intratbecally (i.t.). However, the ED50 for i.t. thapsigargin was the same in tolerant and nontolerant mice, suggesting the involvement of L-type channels rather than a nonspecific effect of raising calcium. To assess whether the number of L-type channels is altered by morphine, radiolabeled nitrendipine binding studies were performed using the spinal cord and pooled brainstem/striatum from morphine-treated and control mice. Binding site number and affinity were determined using Scatchard analysis for the following timepoints: 20 minutes and 60 minutes after subcutaneous injection of an ED_{80} dose of morphine or vehicle, as well as after four days of chronic administration, and after naloxone-precipitated withdrawal. Although some changes were observed in the affinity of nitrendipine for its receptor, a 'significant change in these measures was found only following naloxone administration, which produced increases in binding site number in both chronic placebo- and morphine-treated mice. Phosphorylation by CAMP-dependent protein kinase has been demonstrated to potentiate L-type channel activity. Central administration of KT5720, a specific kinase inhibitor, reversed morphine tolerance in mice. Thus it is possible that with tolerance development these channels are not upregulated but are functionally altered by phosphorylation.

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METOPON AND AN ISOMER OF METOPON ARE SELECTIVE FOR THE MU OPIOID RECEPTOR

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Metopon (5ß-methyl-7,8-dihydromorphinone) and an isomer of metopon incorporating the 5-methyl group into the benzopyran ring were synthesized and characterized for affinity, selectivity and activity in opioid receptor binding and analgesic studies. In competition binding assays with bovine striatal membranes, metopon and its isomer inhibited p-selective binding with K_i values less than 2 nM, but required approximately 70-fold greater concentrations to inhibit δ-- and κ-selective ligand binding. Analgesic properties were measured using the mouse 55°C warm-water tail flick test. Both compounds produced antinociception for up to 60 minutes after i.c.v. injection. Comparison of dose-response lines for morphine sulfate, metopon and the isomer of metopon showed all three compounds produced antinociception with similar D_{50} values. A 24-hour pretreatment of mice with the μ-sclecdve antagonist ß-funaltrexamine inhibited antinociception induced by metopon or its isomer, while δ- and K-selective antagonists produced no significant inhibition of antinociception. These results suggest metopon and its isomer produce antinociception through the μ opioid receptor.

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8-OH-DPAT ATTENUATES THE ANTINOCICEPTIVE EFFECTS OF MORPHINE IN A PRIMATE TAIL WITHDRAWAL PROCEDURE,

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Numerous studies suggest that the serotonergic system has a role in the antinociceptive effects of opioid analgesia. This study examined the effects of the 5-HT_{1A} agonist 8-OH-DPAT in the antinociceptive effects of morphine (MS) in a squirrel monkey tail-withdrawal procedure. In this procedure three monkeys sat in a chair, restrained at the waist with their tails hanging freely. During a test session the lower 4 cm of each monkeys tail was placed in a thermos with either 32-37° C (non-noxious) or 52° C (noxious) water. The latency to withdraw their tails from the water was measured, with a cut off time of 20 s to prevent tissue damage. The mean control latency to withdraw the tail was 19.7 s for the 32-37° C water and 2.5 s for the 52° C water. When given alone, MS (0.3-5.6 mg/kg, 30 minute pretreat) dose-dependently increased the latency to withdraw the tail from the 52° C water and had no effect on the latency to withdraw the tail from the 32-37° C water. When given alone, 8-OH-DPAT (0.001-0.03 mg/kg, 30 minute pretreat) dose-dependently decreased the latency to withdraw the tail from the 32-37° C water, and had no effect on the latency to withdraw the tail from the 52° C water. When the MS dose-effect curve (52° C water) was redetermined in combination with a dose of 8-OH-DPAT that did not alter responding when given alone, 8-OH-DPAT (0.001 mg/kg) shifted the MS dose-effect curve approximately one-half log unit to the right. These results suggest a role for the 5-HT_{1A} system in the antinociceptive effects of MS in response to a noxious thermal stimulus.

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ANALGESIC EFFICACY OF TRAMADOL HCL AND ACETAMINOPHEN WITH CODEINE IN POSTSURGICAL PAIN

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Tramadol hydrochloride is a centrally acting analgesic. It derives its activity from attachment to the mu-receptor and blockage of norepinephrine and serotonin reuptake. The purpose of this single dose, double-blind study was to compare the analgesic efficacy of tramadol HCl 100 mg with the combination of acetaminophen 600 mg/codeine phosphate 60 mg and placebo in 120 inpatients with moderate to severe postsurgical pain secondary to cesarean section or gynecological surgery. Treatments were compared over a six hour period using standard scales for pain intensity and pain relief, and the patient's overall assessment of the study medication. The two active treatments were significantly superior to placebo over the six hour period, as well as with respect to the summary measures SPID, TOTPAR, and the patient's global assessment of the study medication. Tramadol HCl was significantly superior to placebo beginning at hour one for relief and hour two for PID and continuing through hour six. The acetaminophen/codeine combination was significantly superior to placebo beginning at 0.5 hours and continuing through hour six. The combination of acetaminophen/codeine was also significantly better than tramadol HCl beginning at 0.5 hours through hour three for relief, and at hour one and hour two for PID. Tramadol 100 mg and the combination of acetaminophen 600 mg with codeine 60 mg are effective analgesics for the treatment of postsurgical pain. No serious adverse events were reported in this patient population.

RESPIRATION IN RHESUS MONKEYS DURING MORPHINE WITHDRAWAL

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These experiments explored the utility of respiratory measures as non-invasive indices of opioid dependence in monkeys, based on results of an earlier study in humans demonstrating that hyperventilatory responses to CO_2 are increased during morphine withdrawal (Martin, *et. al.,* JPET 162:182, 1968). Three rhesus monkeys received 3.2 mg/kg morphine as a single daily injection; this dose was later increased to two daily injections in two monkeys. Previous studies demonstrated that naltrexone increases the rate of respiration in these monkeys but has little effect on tidal volume. The highest dose of naltrexone tested, 0.01 mg/kg, increases breathing frequency from 27.9 ± 1.1 to 51.0 ± 3.1 breaths/minute in the presence of normal air. Responses to 1%, 3%, and 5% CO_2 are not significantly altered during naltrexone-precipitated withdrawal. Likewise, responsiveness to CO_2 is not increased when the single daily injection of morphine is withheld for 24, 48, or 72 hours. Respiratory responses to CO_2 were also assessed for 28 days following cessation of the twice daily injections of morphine. Changes in responses to CO_2 are not evident up to 28 days after morphine. However, breathing frequency is increased during morphine abstinence; a peak effect (54.1 ± 11.3 breaths/minute) is seen at 48 hours after the last morphine injection. This effect gradually subsides, and by day 28 after morphine, the mean respiratory rate is 23.5 ± 1.0 breaths/minute. Thus, these data do not support the findings of Martin, *et. al.,* however, they do demonstrate that respiration rate is altered by morphine withdrawal.

BEHAVIORAL MEASURES OF ANXIETY DURING OPIOID WITHDRAWAL

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Heightened anxiety is a major component of the withdrawal syndromes associated with ethanol and sedative hypnotic medications. Because of the importance of GABAergic neurons in mediating certain opioid effects, we investigated changes in behavioral measures of anxiety during opioid withdrawal. Long Evans rats received continuous infusions of morphine sulfate at 6.4 mg/kg-hr delivered by osmotic pump over seven days while control animals received inert implants. During the first three days of withdrawal, the number and time of entries into the open arms of a plus-maze was recorded. Both social and aggressive behaviors were scored during pairings of groups of two socially naive animals. Body weight was significantly reduced in morphine treated animals prior to and during withdrawal. Both the number of entrics into open plus-maze arms and the time spent in open areas increased over the three days of testing. However, no difference in plus-maze activity was detected between morphine treated and control subjects. Throughout testing, social interaction time was longer in pairs that contained at least one subject undergoing withdrawal. This trend did not reach significance on days one and two of testing. On the third day of testing, social interaction time was significantly greater in pairs of withdrawn and control subjects, compared to pairs with two control subjects. In conclusion, behavioral measures of anxiety are not increased during opioid withdrawal.

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ROLE OF DELTA-OPIOID RECEPTORS ON THE AVERSIVE STIMULUS EFFECTS OF MORPHINE WITHDRAWAL IN RATS

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The role of delta-opioid receptors in mediating both the physical and aversive effects of morphine withdrawal was examined by use of place preference conditioning. Male Sprague-Dawley rats (250 - 300 g) were made physically dependent by s.c. implantation of two 7.5 mg morphine pellets. Single trial place conditioning with the opioid receptor antagonist naloxone (0.001 - 1.0 mg, s.c.) and the delta-opioid receptor antagonists naltrindole (0.1 - 3.0 mg/kg, s.c.) and naltriben (0.1 - 3.0 mg/kg, s.c.) were conducted on Day 4. Physical signs of withdrawal were also quantified. Tests of conditioning were conducted on Day 5. Naloxone in doses of 0.01 - 1.0 mg/kg produced significant conditioned place aversions in morphine-implanted animals. A dose of 0.01 mg/kg failed to produce any physical withdrawal signs whereas higher doses resulted in wet dog shakes, body weight loss, teeth chattering and diarrhea. No such effects were observed in control (placebo-implanted) animals. Such treatment also resulted in dose-related conditioned place aversions. The administration of the delta-opioid antagonists, naltrindole and natriben, failed to induce ptosis and diarrhea, and the incidence of other withdrawal signs was markedly less than that produced by naloxone. Both naltrindole and natriben produced marked dose-related conditioned place aversions and the magnitude of these effects did not differ from that produced by low doses of naloxone. These findings demonstrate that the selective blockade of either delta- or mu-opioid receptors is sufficient to induce aversive effects in morphine-dependent animals and that such effects can occur in the absence of a quantifiable physical withdrawal syndrome. Furthermore, they indicate a differential role of delta-opioid receptors in mediating psychic as compared to physical dependence upon morphine. They also indicate that the symptoms associated with precipitated morphine withdrawal differ depending upon the opioid antagonist employed.

MODIFICATIONS OF μ-OPIOID AGONIST-INDUCED LOCOMOTOR ACTIVITY AND PHYSICAL DEPENDENCE BY DIABETES

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We examined the locomotor-enhancing action of μ-opioid receptor agonists, such as morphine and [D-Ala^2,N-MePhe^4, Gly-o1^5]enkephalin (DAMGO), and physical dependence on morphine in diabetic and non-diabetic mice. Morphine (5-20 mg/kg, s.c.) and DAMGO (1-4 nmol, i.c.v.) had a dose-dependent locomotor-enhancing effect in both non-diabetic and diabetic mice. The locomotor-enhancing effects of morphine and DAMGO were significantly less in diabetic mice than in non-diabetic mice, and were significantly reduced following pretreatment with either ß-funaltrexamine (20 mg/kg, s.c.), a selective μ-opioid receptor antagonist, or naloxonazine (35 mg/kg, s.c.), a selective μ-opioid receptor antagonist. Both diabetic and non-diabetic mice were chronically treated with morphine (8-45 mg/kg, s.c.) for five days. During this treatment, neither diabetic and non-diabetic mice showed any signs of toxicity. After morphine treatment, withdrawal was precipitated by injection of naloxone (0.3 - 10 mg/kg, s.c.). Several withdrawal signs, such as weight loss, diarrhea, ptosis, jumping and body shakes, were observed following naloxone challenge in morphine-dependent non-diabetic mice. Although morphine-dependent diabetic mice showed greater weight loss than non-diabetic mice, the incidence of jumping and body shakes following naloxone challenge in diabetic mice were markedly lower than that in non-diabetic mice. These results suggest that diabetic mice are selectively hyporesponsive to μ-opioid receptor mediated locomotor-enhancement. Furthermore, diabetes may affect μ-opioid receptor-mediated naloxone-precipitated signs of withdrawal from physical dependence on morphine.

EFFECT OF DIABETES ON LOCOMOTOR ACTIVITY IN MICE

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Locomotor activity in mice has been shown to be modulated by endogenous opioidergic systems. We previously reported that diabetic mice are selectively hyporesponsive to μ-opioid receptor-mediated antinociception, while they are hyperresponsive to δ-opioid receptor-mediated endogenous antinociception, as compared to non-diabetic mice. Thus, functional abnormalities in the opioidergic system of diabetic mice may alter their locomotor activity. To test this hypothesis, the effect of diabetes on locomotor activity in mice was examined. Male ICR mice were rendered diabetic by an injection of streptozotosin (200 mg/kg, i.v.). Spontaneous locomotor activity in diabetic mice was significantly greater than that in non-diabetic mice. The rate of dopamine turnover in the limbic forebrain of diabetic mice was significantly higher than that of non-diabetic mice. SCH23390, a selective dopamine D_1-receptor antagonist and quinpirole, a selective dopamine D_3-receptor agonist, significantly reduced spontaneous locomotor activity in diabetic mice, but not in non-diabetic mice. Spontaneous locomotor activity was also reduced by pretreatment with the naltrindole, a selective δ-opioid receptor antagonist, and 7-benzylidenenaltrexone, a selectiveδ_1-opioid receptor antagonist only in diabetic mice. These results suggest that the enhanced locomotor activity in diabetic mice may result from increased dopamine neurotransmission, which might be due to an increase in dopamine release in mesolirnbic dopamine system. The increased dopamine neurotransmission in diabetic mice may be caused by up-regulated δ-opioid receptor-mediated function.

W.H.O. GLOBAL COCAINE PROJECT

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The WHO/UNICRI Cocaine Project consists of Key Informant Studies, a Natural History Study, descriptive Country Profiles, and a comprehensive search of the scientific literature. Between 1992 and 1994, information was collected from 22 sites in 19 countries about: who uses the drug, what effects cocaine has on users, and bow governments have responded to cocaine use. The Center for Alcohol and Addiction Studies at Brown University served as the coordinating center for the four U.S. Key Informant Study sites. Structured interviews with consultants were conducted face-to-face using an interview that evaluated the following topics: patterns of cocaine and other drug use, consequences of cocaine use, availability of cocaine, current responses to the use of cocaine and general overview. Most consultants reported that cocaine was used by people from all socio-economic and racial/ethnic groups. Cocaine was easy to obtain, with purchases only taking a few minutes to complete. While consultants appeared to be aware of three routes of administration (snorting, smoking, and injecting), they reported snorting and smoking to be the most common. Consultants also noted that those users who experience the greatest problems as a result of their cocaine use are likely to be crack users (*i.e.,* cocaine smokers). Consultants frequently commented on the association between alcohol and cocaine use. Consultants reported that cocaine and sex are related and seemed to concur that, in low doses cocaine could function as an aphrodisiac but in higher doses cocaine was likely to interfere with sexual interest and performance. Negative consequences were widely perceived as more common for intensive, high-dosage users. Regarding negative consequences of cocaine use, respondents most often noted financial and legal problems. Other negative consequences, such as medical emergencies and fetal damage, were rarely mentioned. High-dosage users were also perceived as experiencing mental health consequences including paranoia or, less often, dysphoria, depression, anxiety, loss of cognitive skills, aggression or social withdrawal. It was noted that users rarely entered treatment volunlarily and treatment was often reported to be difficult to access for the high-dosage users most in need.

A PROSPECTIVE STUDY OF BEHAVIORAL REPERTOIRE AND THE RISK OF STARTING DRUG USE IN THE EARLY TEEN YEARS

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Testing hypotheses on reinforcers in the early tecn behavioral repertoire that might promote or compete with drug-taking, we have found predictable associations in cross-sectional interview data from a predominantly African-American epidemiologic sample of about 1500 urban youths. For example, urban youths spending large blocks of time at church or in other religious activities were unlikely to have become drug-takers. To test these hypotheses more rigorously, we re-contacted this sample gathered data prospectively, and performed regression analyses. Data from assessments made in 1993 and repeated in 1994 were used to estimate risk of starting to take drugs in relation to behavioral repertoire at baseline in 1993. The analyses focused on 767 participants age 13-16 years who had not started illicit drug use prior to the 1993 baseline. An estimated 16 percent started drug-taking between 1993 and 1994. The prospective analyses did not confirm all previously observed cross-sectiona1 associations, but the inverse association involving religion was robust. Compared with all others, youths more heavily involved in church or other religious activities were one-third to 1/2 as likely to initiate illicit drug use ($p<0.01$). The estimates changed very little when multiple logistic regression was used to hold constant teen and pre-teen characteristics that might confound observed associations between behavioral repertoire and risk of drug use. By probing mechanisms that produce this association, we seek general principles for preventive interventions directed toward the behavioral repertoire.

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BEHAVIOR PROBLEMS OF CHILDREN OF DRUG ABUSERS

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We tested whether children of drug abusers (CDAs) receiving treatment for cocaine or opiate dependence would have more problems than demographically matched children from two comparison groups: referred children (RCs) and nonreferred children (NRCs). Eighty-seven patients from three sites completed the Child Behavior Checklist (CBCL) about 133 children. Sites included Burlington, VT, Camden, NJ, and Houston, TX. 28% of CDAs were deviant (284th %ile) on total problems, and 19% were deviant (≥95th %ile) on Delinquent Behavior. CDAs scored higher than NRCs on Thought Problems, Attention Problems, Delinquent Behavior and Aggressive Behavior. More CDAs than NRCs were rated in the clinical range on Anxious/Depressed, Attention Problems, Delinquent Behavior, and Aggressive Behavior. However, RCs scored higher than CDAs, and more were rated in the clinical range on all syndromes. CDAs from VT scored higher than those from TX and NJ on Somatic Complaints and Delinquent Behavior. Children of female opiate abusers had higher scores on Somatic Complaints than children of male opiate abusers or cocaine abusers. Seventeen percent of the CDAs had been referred for mental health services in the previous 12 months, but only 30% of those rated in the clinical range on the CBCL had been referred. Thirty-seven percent of the sample appear to be at risk based on their parent's report on the CBCL and/or referral for mental health services. Results suggest that CDAs are at particular risk for externalizing problems, and that they have unmet mental health needs. Data currently being collected from teachers and coparents will be used to validate these findings.

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TEMPERAMENT AND LIABILITY TO EARLY AGE DRUG USE

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This study extends previous research that has shown the greater importance of difficult temperament in parents and offspring compared with paternal lifetime history of substance abuse as a salient correlate of risk factors for drug abuse (Blackson, 1994). Individual, family, and peer risk factors were obtained from 10-12 year old sons of substance abusing (n = 28) and normal fathers (n = 64) to predict their subsequent drug use at 12-14 years of age. Multivariate multiple regression path analysis was used to obtain the following results: Fathers' difficult temperament scores predicted sons difficult temperament scores. Sons' difficult temperament scores were significantly associated with more parental maladaptive discipline, family dysfunction and deviant peer affiliations. Also, the conjoint influence of difficult temperament in fathers and sons predicted sons' cognitive misattribution scores that in turn mediated the effect of sons' difficult temperament scores on their peer delinquency and acceptance of deviancy scores. Moreover, the effect of sons' affiliation with peers engaged in delinquent behaviors on their subsequent drug use was mediated by their acceptance of deviance as normative. Twenty-nine percent of the variance on sons' *Peer Delinquency Scale* scores and 26% of the variance on sons' drug use scores was explained by the full model ($F = 48.01$, $p < .001$). Also, sons scoring 1SD above the *M* on difficult temperament where differentiated from sons scoring 1 *SD* below the *M* on difficult temperament on six out of eight of the risk factors. Paternal SA+/SA- status differentiated the boys on only one out of eight of the risk factors. Further, a father-son temperament incongruity score computed at time one explained 14% of the variance on sons drug use scores at time two. The findings suggest that primary prevention programs that incorporate temperament counseling may attenuate the liability to drug abuse in children having a difficult temperament by redirecting a deviant developmental trajectory toward a more normative outcome.

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DRUG USE PATTERNS AMONG HIGH SCHOOL STUDENTS IN VALENCIA, SPAIN

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Periodic assessment of drug use patterns among different age groups and in different geographical areas is one of the priorities of the United Nations. The aim of the present study was to determine the drug use patterns among adolescents in Valencia, Spain. Between February and March, 1994 a survey was carried out among a proportional sample of high school students stratified by gender, school type (public-private) and type of education. Drug-use patterns were obtained through an anonymous self-administered Health-Questionnaire consisting of 138 items. Statistical analysis was performed using the X^2 test for categorical data and the two-tailed Student's *t* test for comparison of means with interval data. Out of a total 1609 questionnaires, 92 were rejected due to incomplete responses. The age of the sample ranged 13-18 years, with a mean of 14.56 years (S.D.=1.01). Overall, the use of legal and illegal drugs were more frequently reported by males of a higher economical status, from dysfunctional families, and typically on weekends. However, the percentage of females reporting daily tobacco smoking was higher than that of males (CI=95%: 1.13-2.08; $p<0.0001$). A multivariate analysis was performed in order to uncover a complex relationship that could explain the rates of marihuana use. This multivariate model was best when grouping the following variables: gender, age (14-16 years), tobacco use (five intervals) and alcohol use (five intervals). The results showed a probability distribution adjusted to the sample of multiple R=0.609. Thus, in 61% of cases, marihuana use could be related to the concentration of males with frequent tobacco and alcohol use in early periods of adolescence. Considering the relevance of the problem and the age of the sample, it is evident that these students would benefit from active educational programs that include discussion of alcohol and tobacco use in addition to illegal drug use, and that stimulate healthy life-styles.

TOBACCO, ALCOHOL, AND DRUG USE IN 8-16 YEAR OLD TWINS. THE VIRGINIA TWIN STUDY OF ADOLESCENT BEHAVIORAL DEVELOPMENT

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Tobacco, alcohol, and drug use data were collected from the Child and Adolescent Psychiatric Assessment (CAPA) on a representative population sample of twins as part of the Virginia Twin Study of Adolescent Behavioral Development, Using both self-report and parental-report are presented from the first wave of data collection on 1,412 male and female twins, ages 8 through 16. To examine the contribution of genetic and environmental factors in current lifetime tobacco, alcohol, and drug use, and test competing hypotheses about their relative influences, structural equation models were applied to the twin data. Variation in tobacco use (both ever and in the last three months) was explained for the most part by genetic factors with heritabilities of .85 and .88 respectively. For alcohol use the role of genes and environment changed according to the situation. Whether twins ever used alcohol appeared to be influenced by the environment, 65% of the variation by shared environmenral influences and 35% by unique environmental factors. Ever using alcohol without permission of a responsible adult was almost equally mediated by genes and shared environment (42% and 36% of the variation). Genes predominantly influenced current use of alcohol (h^2 = .82). The role of unique environmental factors decreased and that of genetic factors increased with increasing severity of alcohol use. Lifetime drug use (*i.e.,* assessing all classes of drugs) and marijuana use showed genetic heritabilities of .44 and .31 respectively, with the shared environment accounting for 47% and 61% of the variation. Prevalence rates on use of tobacco, alcohol, and drugs show that children using any of these substances at age 12. Rates rapidly increase for tobacco use from age 13 onwards, for alcohol use around age 14 and for drugs even later, with rates for girls being slightly lower than those for boys. Of the 16 year old boys 40% have ever used tobacco, 60% alcohol, and 15% other drugs. The percentages for 16 year old girls are 24%, 48%, and 12% respectively.

USING ECA SURVEY DATA TO IDENTIFY PROSPECTIVE PREDICTORS OF STARTING AND STOPPING DRUG USE

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An important use of the Epidemiological Catchment Area (ECA) survey is when reports of events at the initial interview are used to predict reports at a second interview conducted a year later (*e.g.,* Catalano *et. al,* 1993). Using that same approach, this study examined whether starting or stopping drug use was predicted by gender, age, race, welfare status, employment, education, social-economic status (SES), a significant other, or DSM-III-R criteria for phobia, panic disorder, mania, schizophrenia, depression, anorexia and anti-social personality disorder. Data from individuals who were not using and using drugs at the initial interview, but who had started and stopped at the time of the second interview were selected from approximately 16,600 participants of the survey. Logistic regression analyses were used to examine the relation between reports of events made at the fist and second interviews. The likelihood of starting to use any drug increased for males relative to females. for those without a significant other relative to those with one, and who had lower SES relative to higher SES. Additionally, the likelihood of starting to use alcohol was greater for low SES, those currently on welfare or without a significant other, and for starting amphetamine or cocaine greater for those without a significant other. Individuals meeting DSM-III-R criteria for obsessive compulsive disorder were likely to start cannabis, while those meeting the criteria for schizophrenia were more likely to start both stimulants and sedatives. The likelihood of stopping cannabis, and cocaine use was greater for females than males. The likelihood of stopping stimulant use was greater if the individual had a significant other and if criteria for depression was met. Overall, these data are consistent with the notion that individuals with fewer non-drug reinforcing events are more likely to start and less likely to stop drug use.

ASSESSING THE ACCURACY OF SELF-REPORTED COCAINE USE: METHODOLOGICAL ISSUES WITH UNDERREPORTING OF USE

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As part of a study of cocaine users' treatment outcomes, a random sample of 296 subjects provided urine specimens after completing a face-to-face interview, which included information on recent drug use. Respondents were not informed of the urine testing until after they completed the interview. Cocaine was the most frequently detected drug along 43.9% of the respondents whose urine test was positive for one or more of eight drugs tested. There was 69.3% agreement between the results of urine testing and self-reported use in the past 72 hours; however, only 25.7% of those who tested positive for cocaine reported using this drug in the past 72 hours. Nearly half (49.5%) of those who were positive for cocaine reported weekly or more frequent use in the past year, a key measure in outcome studies. Logistic regression models indicated that those who were not married, had been in treatment for shorter periods, and had not received additional drug treatment subsequent to the episode defining study eligibility were most likely to underreport use. Unlike the univariate results, treatment modality was not significant in the multivariate models, suggesting other factors (particularly time in treatment) were related to underreporting. No support was found for the hypothesis that underreporting would be more likely among those who are employed or under criminal justice supervision at the time of the interview because of the potential negative consequences of reporting drug use.

BEHAVIORAL SENSITIZATION TO NORNICOTINE: LACK OF CORRELATION WITH [^{3}H]NICOTINE BINDING IN RAT WHOLE BRAIN

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We hypothesize that nicotine metabolites contribute to tobacco's abuse liability. Nicotine (1 mg/kg), S(-) or R(+)nornicotine (1-10 mg/kg) or vehicle was administered (s.c.) to rats once every 48 hours for a total of eight injections. Locomotor activity was measured during 50 minute sessions immediately following drug administration. Thus, chronic nicotine produced behavioral sensitization, whereas chronic nornicotine did not. When the groups were challenged with nicotine (1 mg/kg) on the last experimental day, rats chronically administered nornicotine responded as if administered chronic nicotine, *i.e.,* behavioral sensitization was then observed. Cotinine (0.3-10 mg/kg) was without effect either after acute or chronic administration. Moreover, no dose of cotinine was found to produce sensitization on the nicotine challenge day, *i.e.,* no behavioral sensitization. [3H]Nicotine binding parameters were determined in whole brain from rats administered saline, nicotine (1 mg/kg), S(-)nornicotine (10 mg/kg) or R(+)nornicotine (10 mg/kg). No differences were found in Kd ((2 nM) or Bmax ((50 fmol/mg protein) betwecn groups. Thus, nornicotine stimulated the mechanism responsible for behavioral sensitization, without overtly eliciting sensitization itself. Also, sensitization was observed following chronic nicotine or nornicotine without a change in the number of [3H]nicotine binding sites in whole brain.

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THRESHOLD DOSE FOR NICOTINE DISCRIMINATION AND REINFORCEMENT IN ANIMALS AND HUMANS

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It has been reported (Benowitz and Henningfield, 1994) that the nicotine delivery of cigarettes be reduced to the point that cigarettes could be considered non-pharmacologically addicting. However, there continues to be uncertainty regarding an appropriate threshold for the non-pharmacologically addictive dose. Studies of nicotine's reinforcing and discriminative effects may be useful in this analysis. We present an interpretive review of 31 studies published in scientific journals from 1967-1993. We found that the threshold dose was as low as 0.025 mg/kg in drug-discrimination studies, and 0.075 mg/kg in self-administration studies. Human (75 kg) equivalent doses are 1.875 mg and 0.5625 mg, respectively. To convert these doses to cigarette-equivalent doses, we followed a model used by Yanagita and colleagues that was based on parameters of Russell *et. al.,* (1980). Assuming that a 1.0 mg IV infusion produces a 6.6 ng/ml blood nicotine concentration and that cigarettes yielding 1.25 mg nicotine produce blood concentrations of 4-72 ng/ml, the cigarette would have to yield 0.215 and 0.0645 mg to produce discriminative and reinforcing effects, respectively. Interestingly, this suggests that the threshold for nicotine reinforcement is lower than the threshold for discrimination. Thus, the present analysis suggests that the nicotine delivery threshold of a non-addictive cigarette might have to be lower than 0.0645 mg. We used 1.25 mg nicotine as the average cigarette yield; however, individual yields vary considerably, and smokers may obtain up to 4.0 mg from most presently available cigarettes. Most of the studies were conducted using nonhumans (29/31). Although there is some consistency across species, there is clearly a need for more human studies.

DEFINING THE TREATMENT ENVIRONMENT AND ITS IMPACT ON RETENTION

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The residential therapeutic community is an evolving modality that is continually adapting to address the needs of the broad spectrum of individuals entering treatment. Originally established for the treatment of adult, male opioid abusers, TC clients now present with problems with substances other than opioids, and a significant minority are females and/or adolescents. Although, in general, TCs have a common underlying philosophy and perspective, there is diversity in terms of clinical structure, resources and environment. The current study examines the relationship between the treatment environment and client retention. The program sample includes six adolescent TCs (9 sites), involving 938 admissions during the study period. The programs differ on a number of dimensions including recommended length of treatment, physical setting, staffing (training, cohesiveness, etc.) and resources. **An Environmental Risk Index** was developed which reflects the perceived level of environmental risk for client dropout at each site. The Index assessed the programs along such parameters as staff characteristics (cohesiveness, caring, accessibility), location (rural or urban), rules and regulations (stringency and consistency of application), and level of control. Each program/site was given a score in relation to the other sites so that a rank ordering of programs in terms of perceived environmental risk for client dropout was established. Dropout/retention rates varied considerably among the different programs/sites; 90 day retention rates ranged between 39% and 97%. The Environmental Risk Index, although entered into the regression equation last, was a significant and large predictor of retention. Continued research is planned to develop a clinical/research instrument for assessing the treatment environment to enhance retention in TCs with potential generalizability to other settings.

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UNDER-REPRESENTATION OF CYTOCHROME P450 2D6 (CYP2D6) DEFICIENT GENOTYPE IN DRUG DEPENDENCE: INITIAL RESULTS

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The drug metabolizing enzyme CYP2D6 is polymorphic (*e.g.,* 7% of Caucasians lack the enzyme); found in liver and brain; metabolizes a number of drugs of abuse (*e.g.,* codeine, metbarnphetamine, nicotine but not ethanol, cocaine or heroin). Several variant forms with different catalytic activities have been identified in individuals with the enzyme. Therefore, the risk of drug dependence might be related to CYP2D6 relative activity and genotype for substrates of the enzyme.

Unrelated Caucasians (never drug dependent [N = 75] and DSM-IIIr dependent individuals: alcohol [N = 81]; cocaine [N = 73]; prescription opiates [N = 78]; nicotine [N = 83]) were genotyped by CYP2D6 mutation specific PCR amplification. The relative frequencies of the B/B poor metabolizer genotype were 8.0, 2.5, 2.5, 3.8, and 2.4% for the groups as listed respectively (p = 0.2; dependent vs. nondependent). These results are preliminary because of the relatively small numbers of subjects recruited to date. The consist pattern for drugs of abuse that are and are not substrates for CYP2D6 is as yet unexplained. This raises the possibility that CYP2D6 has some alternate intrinsic function alone or it co-segregates with gene(s) that alter the risk of dependence.

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DEVELOPMENTAL CHANGES IN PRE- AND POSTSYNAPTIC COMPONENTS OF SEROTONIN SYSTEMS AFTER PRENATAL EXPOSURE TO COCAINE

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These studies investigate the occurrence and longevity of biochemical and functional changes in pre-and postsynaptic components of serotonin (5-HT) pathways induced by prenatal exposure to cocaine. Pregnant Sprague-Dawley rats were administered saline (1 ml/kg) or (-)cocaine (15 mg/kg, s.c., b.i.d.) from gestational day 13 through 20. Male progeny were studied at postnatal days 28 and 70, representing pre- and postpubescent ages, respectively. Alterations in 5-HT systems were assessed by measuring neuroendocrine responses to challenge with a 5-HT releaser or 5-HT agonists as well as levels of 5-HT and 5-HIAA (5-hydroxyindoleacetic acid) and the density of 5-HT recognition sites. In prepubescent cocaine-exposed progeny, the ability of the 5-HT releaser, p-chloroamphetamine (PCA), to elevate plasma ACTH but not renin was markedly attenuated (-32%). In contrast, the ACTH and renin responses to maximally effective doses of the $5HT_{1A}$ and $5\text{-}HT_{2A/2C}$ agonists 8-OH-DPAT and DOI, respectively, were potentiated. In postpubescent cocaine-exposed progeny, ACTH and renin responses to PCA were markedly reduced (-43% to 50%); there were no changes in $5\text{-}HT_{1A}$ or $5\text{-}HT_{2A/2C}$ mediated ACTH or renin responses. These data: (1) demonstrate differential changes in pre-and postsynaptic 5-HT components at pre- and postpubescent ages in male progeny exposed prenatally to cocaine, (2) demonstrate the necessity to utilize pharmacological or other types of challenge tests to identify neurochemical teratogenic effects of drugs which may not be apparent from the measurement of basal parameters alone and (3) indicate the potential clinical utility of neuroendocrine challenge tests to assess the functional consequences of prenatal exposure to cocaine.

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EFFECTS OF IN UTERO EXPOSURE TO REGIMENS OF 1,1,1-TRICHLOROETHANE INHALATION EXPOSURE IN MICE

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Pair-fed pregnant mice were untreated or exposed to either 2,000 ppm 1,1, 1-trichloroethane (TCE) or filtered air overnight for 17 hours during gestational days 12-17. Offspring were examined for developmental landmarks and tested for reflex, coordination and neuromuscular development from postnatal day (PND) 1-14 and activity on PNDs 23-25. Maternal weight gain, litter size, sex ratio, pup birth weight and pup mortality were similar. Pups exposed to TCE gained less weight than air only or control pups from PND 2-14. TCE offspring had significant delays in eye opening, pinnae detachment and incisor eruption, demonstrated weaker grip strength and delays in acquiring the righting reflex, negative geotaxis and inverted screen tasks. Post-weaning observations of motor activity did not differ among groups. In order to develop an animal model more closely mimicking a pattern of solvent abuse, pregnant mice were exposed to 8,000 ppm TCE three times/day for one hour during gestational days 12- 17. Offspring were assessed from PND 1-21 using a variety of developmental and behavioral tests. Maternal weight gain, litter size, litter weight, sex ratio and pup mortality did not differ. Pups exposed to TCE in utero gained less weight relative to control pups from PND 1-20. TCE offspring had significant delays in eye opening, pinnae detachment and incisor eruption. Compared to controls, TCE offspring displayed weaker forelimb grip strength and rooting distance and delays in acquiring the righting reflex and negative geotaxis tasks. Post-weaning observations of activity, nociception (tail flick and hot plate) and passive avoidance learning did not differ between groups. These data provide evidence for the behavioral and developmental teratogenicity of prenatal TCE exposure during the last week of gestation.

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OPIOID AND NON-OPIOID EFFECTS OF κ AGONISTS ON THE FETAL HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

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Proper functioning of the fetal HPA axis is essential in enabling the fetus to appropriately adapt to stressful stimuli. As exogenous administration of opioids is known to modulate the HPA axis, there arises the potential for jeopardising fetal well-being with the use of opioids in pregnancy. We have previously demonstrated in the late-term fetal sheep (>0.8 term) a significant increase in plasma *ir*-ACTH and *ir*-cortisol with the administration of morphine as well as p-selective opioid agonists. This study was undertaken to determine the effects of κ-agonists on the fetal HPA axis and to better elucidate the possible role of endogenous opioids in regulation of pituitary-adrenal function. The highly selective κ agonist, U50,488H (1mg/kg, iv) caused an immediate and highly significant increase in plasma *ir*-ACTH with a concurrent rise in *ir*-cortisol. which continued to rise over one hour. This effect was reversible by naloxone (12 mg/h, iv), suggesting an opioid mechanism. Interestingly, dynorphin (dyn) A(1-13)(500 μg/kg, iv) caused a naloxone insensitive rise in *ir*-ACTH and *ir*-cortisol, comparable in magnitude to US0,488H, but reaching its peak at 15 minutes. To investigate this non-opioid component of dyn A(1-13), we administered dyn A(2-17), which does not show activity at the opioid receptor. Because the effects of dyn A(1-13) could not be mimicked by dyn A(2-17), a non-opioid mechanism distinct from that of dyn A(2-17) is suggested. Finally, the huge magnitude of ACTH increase stimulated by κ agonists gives rise to the possibility of a non-pituitary site of release, such as the placenta.

OPIOID AND NONOPIOID ACTIONS OF DYNORPHIN A (1-13) ON FETAL CARBOHYDRATE METABOLISM

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Dynorphin (dyn) peptides and κ binding sites have been identified in human placental tissues, and the presence of dyn in umbilical vein suggest that it is released into the fetal circulation. However, the functional roles of dyn in the placenta and fetus remain uncertain. In this study, we investigated the effects of dyn on fetal carbohydrate regulation. Intravenous dyn A(1-13) (500 μg/kg) to the fetal lamb resulted in a significant decrease in both plasma glucose (22%) and lactate (15%) levels. Pretreatment with naloxone completely blocked the hypoglycemia but resulted in a significant increase in plasma lactate (43%). Administration of a selective κ agonist (U50,488H, 1 mg/kg) had no effect on plasma glucose but increased lactate levels (29%), which was completely blocked by naloxone. In contrast, the μ agonist (DAMGO, 1 mg/h) decreased both plasma glucose (20%) and lactate (20%) levels. These data suggest that dyn A(1-13) may act via μreceptors to decrease plasma glucose and lactate, and via κ receptors and other nonopioid pathways to increase lactate levels. This nonopioid action of dyn is supported by a similar lactate increase with dyn A(2-17) which does not bind to the opioid receptor. The placenta is known to be a large source of lactate for the fetus, and these data suggest that a possible role for dyn in the placenta might be to regulate lactate release from the placenta which can then subsequently be used by the fetus as metabolic fuel.

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NEGATIVE AFFECT INDUCED BY PRECIPITATED MORPHINE WITHDRAWAL IN THE INFANT RAT

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In a variety of species, including humans, abstinence from opiates in adults induces autonomic symptoms, motor behaviors, and a negative affective state. The neurobehavioral bases of each of these is different. Little attention has been paid, however, to the issue of withdrawal in infants although it is a common consequence of maternal use of illegal and legal drugs. Recently it was shown that infant rats undergo withdrawal from both morphine and methadone and that the abstinence syndrome in the infant rat consists of developmentally appropriate behaviors that are different from the adult. The presence of a negative affective state during opiate withdrawal has not been demonstrated however. In the current studies, we treated infant rats with morphine (3.0 mg/kg b.i.d.) or saline from postpartum day 1 to 7 (P1 - 7) or 8 to 14. On the last two days of the chronic injection regimen, pups were injected with saline or naltrexone to precipitate withdrawal and were exposed to a novel odor for one hour. On the last day of the chronic injection regimen, five hours post-conditioning, pups were given an odor-preference test in which they could spend time near the novel odor (S+) or clean air (S-). Pups chronically treated with morphine exhibited an aversion to the S+ following naltrexone but not saline treatment when tested on P14 but not P7. The ability of infants to learn aversions to stimuli associated with opiate abstinence has important potential consequences for the affective development of the infant and for the mother infant bond.

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DEVELOPMENTAL TOXICITY STUDY WITH LEVO-ALPHA-ACETYLMETHADOL (LAAM) IN TOLERANT RATS

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The developmental toxicity, including teratogenic potential, of LAAM was evaluated in groups (one control and three treatment groups of n = 30 each) of Charles River Crl:CD VAF/Plus female rats. Rats were made tolerant by gradually increasing doses of LAAM over a 12-week period from 2 mg/kg/day until the desired levels of 2,6 and 12 mg/kg/day were achieved. Females were then mated to untreated males and maintained on stabilized levels of LAAM throughout gestation. On gestation day 20, cesarean section was performed and fetuses examined for visceral and skeletal anomalies. Pharmacotoxic signs seen at all doses of LAAM included increased activity and decreased body weight to which tolerance developed, as well as decreased food consumption. Maximum reduction in body weights occurred at 6 mg/kg/day of LAAM, with no further decrease upon doubling the dose to 12 mg/kg/day. No drug-related deaths occurred. Developmental toxicity, evidenced as postimplantation loss, occurred at all levels of LAAM, with an apparent dose-response relationship. Despite clear evidence of both maternal and developmental toxicity, no treatment-related visceral or skeletal abnormalities were observed. The developmental NOAEL of LAAM given daily by savage to tolerant female rats was less than 2 mg/kg/day based on implantation loss. There was no evidence of teratogenic potential.

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PEMOLINE OPEN TRIAL: DRUG-DEPENDENT DELINQUENTS WITH ADHD

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Adolescents with comorbid substance use disorders (SUD) and conduct disorder (CD) have higher rates of attention deficit hyperactivity disorder (ADHD) than youth without CD and SUD. In such youth, comorbid ADHD may contribute to the severity and persistence of SUD. Treatment of ADHD may enhance a patient's ability to utilize substance treatment. Despite this, little is known about the response of ADHD symptoms to psycho-pharmacologic intervention in substance-dependent delinquents. Pilot data are presented on nine male adolescents with CD and SUD in a residential substance treatment program. Patients with child psychiatrist diagnosed ADHD were treated with pemoline. Scores were obtained on the Conners' Hyperactivity Index (CHI) (teacher-rated) and continuous performance tasks (Gordon Diagnostic) at baseline and after about one month of treatment with pemoline. Twenty-four hour physical activity measurements (motility) were also assessed at baseline and one month. The post-medication assessments were obtained after at least one week of pemoline treatment at maximal dosage (1.2-3.3 mg/kg--up to 187.5 mg per day). Eight of nine subject's CHI scores declined from pre- to post-pemoline assessment, and motility levels also declined for eight of nine subjects (Sign test; both $p<.04$). The mean CHI at post-test was 17% lower than at pre-test, while the mean motility level was 11% lower at the post-pemoline assessment. Continuous performance scores did not change significantly. These prelimimary data indicate that pemoline may be a useful treatment for ADHD in substance-dependent delinquents and call for a controlled treatment trial of pemoline in such youth.

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INFLUENCES ON ADOLESCENT SUBSTANCE DEPENDENCE: CONDUCT DISORDER, DEPRESSION, ADHD, AND GENDER

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Substance Dependence (SD) is usually comorbid with Conduct Disorder (CD) in adolescence, but Attention Deficit Hyperactivity Disorder (ADHD) and Major Depression (MDD) are also frequently comorbid with those conditions and may worsen the SD. We hypothesized that CD, MDD, and ADHD might contribute differentially to SD and that these effects might be different in males and females. We examined 171 male and 68 female adolescents with comorbid CD and SD problems using the CIDI-SAM and the Diagnostic Interview Schedule for Children (DISC 2.1). Stepforward multiple linear regressions examined age at intake, age of first CD symptom and severity of each disorder by symptom count. The resulting models diagram significant predictors of SD in order of importance by gender:

MALES: CD + MDD --> SD FEMALES: MDD --> SD

CD severity best predicted SD in males, whereas it did not enter the equation for females. Instead, MDD was the best and only predictor for females, and it secondarily predicted SD in males. Although ADHD and age of first CD symptom are both important predictors when CD severity and MDD are not in the model, their relative contributions are outweighed by the presence of these other variables. This suggests that CD and depression should be considered primary in males. whereas depression alone is key for females, even in the presence of ADHD.

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PREVALENCE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND OTHER DISORDERS AMONG COCAINE ABUSERS

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There is an increasing literature suggesting an association between childhood Attention-Deficit Hyperactivity Disorder (ADHD) and substance abuse, particularly cocaine abuse, but little information on the connection with adult ADHD. Multiple assessments are being used to determine the prevalence of ADHD with respect to gender and ethnicity among treatment-seeking cocaine abusers at three different sites. Assessments include the SCID for DSM-IV (for Axis I and Axis II psychiatric diagnoses), a SCID-like module for adult ADHD, and the Wender Utah Rating Scale. Depending on the degree and severity of symptoms, different categories were used to classify both childhood and adult ADHD. To date we have completed 126 out of 300 interviews. The mean age of participants was 34 years and on average they had last used cocaine 10 days prior to the interview. Twenty-five percent were female and 75% were male. With respect to race, 70% were African-American, 12% were Caucasian, and 18% were Hispanic. Approximately 28% of the individuals interviewed met criteria for some form of childhood ADHD and 74% of those with childhood ADHD had some form of adult ADHD (21% of total sample). In addition, 13% had substance-induced adult ADIHD (*i.e.,* no history of childhood ADHD). Overall, 31% of the total sample had some form of adult ADHD. The prevalence of adult ADHD was slightly higher for men (33%) compared to women (28%) and higher for Hispanics (65%) and Caucasians (40%) relative to African Americans (22%). Other psychiatric disorders were common among this sample, particularly among those with persistent ADHD symptoms into adulthood. Although it is clear that multiple substance dependence was common among all subjects, the numbers are too low to make comparisons between those individuals with ADHD symptoms and those without.

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PLATELET DENSE GRANULE SECRETION IN ADOLESCENTS WITH CONDUCT DISORDER AND SUBSTANCE ABUSE

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Platelet aggregation responses to agonists have been employed as peripheral indices of the physiological responsiveness and density of neurotransmitter receptors, and in investigations of membrane functioning in psychopathological conditions. In particular, there are mechanistic similarities between neuronal secretory and receptor dynamics, and those involved in platelet dense granule secretion. Consequently, we have explored the platelet dense granule secretory responses to various agonists in abstinent male adolescents who meet current psychiatric diagnostic criteria for Conduct Disorder and Psychoactive Substance Use Disorder (CD+/PSUD+) in contrast to controls (CED-/BUD-). The results showed a significant hyporesponsivity among experimental subjects to collagen, thrombin, adenosine diphosphate (ADP), ADP plus 0.2 µgm of serotonin, and ADP plus 1.0 µgm of serotonin. Only dense granule responses to arachidonic acid did not differentiate the groups. Taken together, the lack of agonist specificity suggests that a variation in signal transduction mechanisms could account for the observed reduction in dense granule secretion among CD+/PSUD+ adolescents. Association between dense granule secretory responses and substance use behavior, and comorbid psychiatric conditions are also examined.

URINARY BENZOYLECGONINE LEVELS AS A POST INDICATOR OF RITANSERIN EFFICACY IN COCAINE-DEPENDENCE TREATMENT

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We conducted an eight week double blind, placebo-controlled pharmacotherapy trial of Ritanserin for cocaine dependence. The trial was divided into three phases. In **Phase I,** a baseline stabilization phase, only placebo medication was administered. In **Phase II,** a four week double-blind medication phase, subjects were randomly assigned to either Ritanserin or placebo (N=62). In **Phase III,** a post medication follow-up, we evaluated drug use and drug craving. Urine specimens were collected during phase II, the medication phase, at the interval of three times weekly. During the follow-up period, phase III, urines were collected twice weekly. Urinary levels at the completion of the study showed four distinct categories of patterned excretion: **Theoretical** (positive values at Phase I that decrease to zero during Phase II and III), **Negative** (zero values at Phase I, II, and III), **Negative to Positive** (zero values at Phase I that increase steadily through Phases II and III), and **Positive** (values consistently positive throughout Phase I, II, and III). All urine specimens were analyzed using FPIA. While the outcome of this trial has yet to be finalized, and the medication stratification yet to be determined, distinctly grouped patterns of urinary excretions during phase II and III can be speculated in regards to treatment efficacy, barring expected relapses. Percent wise, the four groups translated to: Theoretical 24.2%, Negative 54.8%. Negative to Positive 1.6% and Positive 19.4% (n=62). Since subjects in the positive grouping may be the most difficult to assess due to varied responses to minimal-to-moderate therapeutic effect, it is well advised to collect several urine specimens over an extended baseline period to identify such subjects.

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SEROTONIN, IMPULSIVITY, AND AGGRESSION IN DRUG DEPENDENCE

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Serotonin's involvement in aggression has been repeatedly shown in both animals and humans. It has been suggested that serotonin's involvement in aggression and several psychiatric disorders may be through an effect on impulse control. More recently serotonin has been implicated as a mediator of drug seeking behavior. This study will test the hypothesis that drug dependent human subjects will be more impulsive, more aggressive, and have decreased serotonergic activity when contrasted with abstinent subjects. These will be measured by behavioral and psychometric tests and a neuroendocrine challenge with the 5-HT1a receptor specific agonist, ipsapirone. Results from twenty-seven subjects tested in laboratory paradigms of aggression and impulsivity show that drug dependent subjects maintain aggressive responding after six sessions of provocation, while abstinent subjects rapidly decrease aggressive responding to continued provocation ($F=4.584$, $p<.001$). No differences in impulsive responding were found. Serum cortisol levels have been measured for four hours after the challenge in only nine subjects. It is too early to make any conclusions, but drug dependent subjects have a slightly greater response (insignificant) than abstinent subjects. Twenty subjects will be tested in each drug use history group. It is believed that drug dependence may be related to a cluster of inter-related factors; altered serotonergic function, increased impulsivity, and increased aggression, but data are only preliminary at this point.

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MEASURES OF AGGRESSION IN RECENT COCAINE ABUSERS

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As part of a continuing effort to determine the effects of cocaine on aggression, we are studying hospital inpatients admitted for cocaine treatment. In the past, in our laboratory, we have found no evidence for increased aggression after either a single dose or repeated intranasal doses of cocaine. As a result, we are now looking at the possibility that chronic abuse of cocaine and the subsequent withdraw may elevate aggressive responding. To do this, the Point Subtraction Aggression Paradigm is being used with three response options available to the subject: (1) point-maintained responding (earning points exchangeable for money); (2) aggressive responding, subtracting points from another fictitious other subject; and (3) escape, avoiding point subtractions. Aggressive responses are engendered by periodic point loss artributed to the fictitious subject. Measurements of aggression are being taken upon admission and then when possible again one week later. Twelve subjects have been tested thus far and there are two important trends in the data. One, subjects reporting recent cocaine use emit fewer aggressive responses than subjects not reporting recent cocaine use. Two, antisocial personality disorder appears to be more predcti ve of aggressive responding than recency of cocaine use. These findings are consistent with our hypothesis that cocaine does not appear to induce aggression, but rather the more important factors are the characlcrislics of the person using cocaine.

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MEASURES OF AGGRESSION, IMPULSIVITY AND CNS SERQTONERGIC ACTIVITY IN MALE PAROLEES

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Thirty males on parole participated after giving their informed consent. Subjects were divided into a violent (n=9) and nonviolent group (n=21) based upon their criminal history. Subjects were excluded if screening indicated any history of medical or psychiatric illness, or recent drug use detected by urine drug screen analysis. Subjects participated for four days. Day 1 consisted of six 25 minute sessions during which aggressive and escape responding were measured using the Point Substraction Aggression Paradigm. Day 2 consisted of up to ten sessions which employed a11 adjusting self-control procedure to measure impulsivity. Days 3 and 4 involved two neuroendocrinc challlenge tests conducted in thc University's CRC. One day subjects were administered placebo and on the other day, buspirone 0.4 mg/kg. To assess CNS serotonergic activity in these subjects serial measures of prolactin were taken to determine the response to the challenge agent, buspirone. The violent and nonviolent groups differed significantly on measures of aggressive responding, impulsivity and prolactin response, as well as psychometric measures of aggression. The violent parolees emitted more aggressive responses, made more impulsive choices, and had a lower CNS serotonergic response to buspirone. These data support the external validity of measures of human aggression obtained under controlled laboratory conditions, and they also suggest behavioral tendencies and biological conditions which may result in increased probabilities of violence, impulsivity and risks for other antisocial behavior such as drug dependence.

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CORRELATES OF VIOLENT BEHAVIOR AMONG RECENT ENROLLEES IN DRUG ABUSE TREATMENT

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The prevalence of and factors associated with violence have been the subjects of much attention recently. This is especially so with respect to domestic violence. As a secondary analysis of a large data set involving 766 patients recently admitted to six NYC methadone maintenance clinics, we analyzed the prevalence of self-reported violent behaviors in the last 30 days and during their lifetime. Each patient was administered the Addiction Severity Index (ASI) at admission to the study and at follow-up every three to four months. We present here the findings of the analyses of the baseline data. The mean age of the study population was 37.15 ± 7.26; 36.6% were women. The population was 52.3% Black, 41.2% Hispanic, and 6.5% White/Other. Fifty-nine (7.7%) of patients reported violent behavior in the last 30 days and 147 (19.2%) during their lifetime. Study subjects who reported a violent behavior in the last 30 days were younger (mean age = 35.3 years; $p = .033$), had fewer years of education (mean = 10.7 years; ns), a lower employment composite score (mean = .8910, ns), a higher family/social support composite score (mean = .3554; $p = .0001$), a higher psychiatric composite score (mean = .4160; $p < .0001$), and a higher alcohol composite score (mean = .1531; $p = .0132$). The Beck Depression Inventory (BDI) indicated that participants who experienced trouble controlling violent behavior were more likely to show moderate depression (20.2 ± 10.8) as compared to those who without such trouble (12.8 ± 9.6). The Michigan Alcoholism Screening Test (MAST) scores also revealed that the participants with a history, of violent behavior were more likely to have a positive screening for alcoholism as compared to participants with non-violent behavior (13.4 vs 9). This preliminary data suggests that the prevalence of recent violent behavior among opioid dependent persons is associated with age, family/social support, legal, psychiatric, and alcohol-related problems. This information would also suggest the targets for interventions to reduce the prospects of violent behaviors among persons with a history of heroin use.

VIOLENCE IN SUBSTANCE ABUSERS

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Substance abuse and violent behavior are frequently comorbid, particularly in cocaine users in urban areas (Lindenbaum *et. al.,* 1989, Murdoch *et. al.,* 1990). Using the Suicide and Aggression Survey (SAS)(Koin *et. al.,* 1992), we tested the hypothesis that violent behavior is more frequent in cocaine abusers as compared with alcohol abusers. Pilot data was collected on 31 consecutive admissions to a VA inpatient alcohol and drug rehabilitation center. SAS data were analyzed from 18 "crack" cocaine dependent patients and nine alcohol dependent patients without other psychiatric comorbidity (DSM IV criteria). Duration of substance use was significantly greater among alcoholics as compared with cocaine addicts ($t=6.71$, $p<.0001$). No differences in "Violence Risk" (VR) or "Lifetime History of Aggression" (LHOA) were found between the two groups. However, when the data were reanalyzed controlling for duration of use, cocaine addicts demonstrated greater mean scores on VR (alc.=5.50, coc.=7.19) and LHOA (alc.=7.52, coc.=15.29) than alcoholics. These differences were not significant.

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THE RELATIONSHIP OF ANTISOCIAL PERSONALITY DISORDER AND SUBSTANCE ABUSE TO COGNITIVE FUNCTIONING AMONG MALE FELONS

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Introduction: Cortical abnormalities have been postulated as a significant etiological component of antisocial personality disorder (APD). The present study investigated the relationship of drug abuse history and APD to neuropsychological functioning and aggressive behavior. **Method:** Incarcerated adult male felons (N=280) completed a neuropsychology and psychopathology evaluation. Using DSM-III-R criteria for substance abuse/dependency and APD, subjects were classified into eight groups: 1) alcohol abusing APD (n=37), 2) alcohol abusing non-APD (n=41),3) cocaine abusing APD (n=23), 4) cocaine abusing non-APD (n=27), 5) polysubstance abusing APD (n=43),6) polysubstance abusing non-APD (n=33), 7) non-substance abusing APD (APD control; n=31), and 8) non-substance abusing non-APD (control; n=55). Subjects were matched on age, education, and IQ. **Results:** No significant differences were observed between substance abusing versus non-abusing APD subjects. Relative to all alcohol and polysubstance abusing groups, both cocaine abusing groups and both control groups exhibited significantly better cognitive functioning. Polysubstance dependent APD subjects performed consistently worse on neuropsychological measures than all other groups. Polysubstance APD subjects also displayed a highly significant relationship between neuropsychological dysfunction and measures of hostile or violent behavior. **Discussion:** Among these incarcerated felons, alcohol and polysubstance, but not cocaine, abuse were associated with greater neuropsychologica1 impairment. Findings support the hypothesis that both drug abuse and APD, in particular the combination of multiple drug abuse and APD, may be reflected in cognitive dysfunction and aggressive behavior. Polysubstance abusing antisocials may represent a population of felons requiring special attention in management issues regarding incarceration and in rehabilitation efforts.

PSYCHOSOCIAL CORRELATES OF MMPI-2 DEFINED PSYCHOPATHOLOGY CLUSTERS AMONG DRUG-DEPENDENT MEN

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Previous studies have assessed MMPI-defined psychopathological subtypes. However, the clinical utility of the MMPI-2 as a tool to guide substance abuse treatment interventions has not been adequately explored. The present study sought to characterize psychopathology subtypes, and identify psychosocial correlates, substance abuse patterns, and external validators of MMPI-2 defined subtypes. The sample consisted of drug-dependent men (N=191) seeking treatment with no current or previous DSM-IV Axis I diagnosis, at least a 9th grade education, a valid MMPI-2 profile, and no cognitive deficits. The K-Means clustering procedure yielded three distinct subtypes. Cluster 1 (n=30), the Severely Disturbed Group, showed clinical elevations (T>65) in the Hysteria, Depression, Hypochondriasis, Psychopathic-Deviate, Paranoia, Schizophrenia, Mania, and Social Introversion scales. Cluster 2 (n=82), the Antisocial-Depressed Group, showed clinical elevations in the Schizophrenia, Psychopathic-Deviate, and Depression scales. Cluster 3 (n=79), the Normal Group, showed no clinical elevations in the MMPI-2 clinical scales. Consistent with the literature, three distinct psychopathology subgroups were identified using the MMPI-2 clinical and validity scales. The clusters were externally validated by the SCL-90-R, the Addiction Severity Index and the Beck Depression Inventory, where subjects in the severely disturbed cluster consistently showed higher levels of psychopathology. Relative to the Normal Group, subjects in the Severely Disturbed cluster also showed higher levels of alcohol intoxication, and more use of amphethamines and hallucinogens. In contrast, the Normal Group reported higher lifetime opiate use and acknowledged more alcohol problems. Regarding problems of daily living, subjects in the Severely Disturbed Groups reported more personal functioning, employment, legal, medical, and psychological problems and more physical and emotional abuse. Psychosocial correlates of psychopathology subtypes as defined by the MMPI-2 may be used to guide treatment interventions. Future studies should assess the long-term substance abuse and relapse patterns among MMPI-2 defined clusters.

ANGER MANAGEMENT, POSTTRAUMATIC STRESS DISORDER, AND SUBSTANCE ABUSE

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Anger control problems complicate substance abuse treatment. Few studies have examined anger management treatments for substance abuse patients. In a previous presentation, we outlined an anger management group treatment for substance abuse patients and presented preliminary outcome data demonstrating its efficacy. Here, we present preliminary findings on the moderating role of combat-related posttraumatic stress disorder (PTSD) on treatment outcome. PTSD is associated with high levels of anger which may require more intensive anger management treatment than those used for substance abuse patients with high levels of anger without PTSD. In a comparison of substance abuse patients with PTSD and substance abuse patients without PTSD, we examined the extent to which patients with PTSD 1) had higher levels of state-anger, trait-anger, and anger-expression at intake, 2) had lower levels of anger-control at intake, 3) dropped out of treatment earlier, 4) showed less decrease in state-anger, trait-anger, and anger-expression across treatment, and 5) showed greater increase in anger-control across treatment. Patients with PTSD did not differ on state-anger, trait-anger, and anger-control at intake, did not drop out of treatment earlier, and did not differ on the extent to which they decreased trait-anger and anger-expression across treatment. Substance abuse patients with PTSD, however, showed higher levels of anger-expression at intake and greater increases in anger-control during the final six weeks of treatment. These findings suggest that anger management treatments developed on substance abuse patients without PTSD can be used effectively for substance abuse patients with PTSD.

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ANTISOCIAL BEHAVIORS AND TREATMENT ENTRY AMONG COCAINE USERS: A POPULATION BASED STUDY

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This study examined the influence that the history of antisocial behaviors may produce in treatment entry among cocaine users, particularly when other drug related problems are present. This study examined whether the self-reported history of antisocial behaviors might hamper cocaine users who have drug-related emotional, interpersonal and/or health problems from entering treatment. The sample consisted of 626 respondents who reported use of cocaine at least once a month in the year prior to the interview obtained from the 1991 and 1992 National Household Survey on Drug Abuse. Using multiple logistic regression to hold constant socio-demographic characteristics and frequency of use, we found that, overall, the presence of drug related problems was associated with entering treatment (emotional OR=6.7, 95% CI=3.4-13.3; interpersonal OR=5.1, CI=2.9-8.8; health-related OR=3.5, CI=2.1-5.7). However, there was evidence of an interaction in which the magnitude of the association of emotional and interpersonal problems with treatment entry is significantly reduced for cocaine users with antisocial behaviors. Among cocaine users with antisocial behaviors, the relative odds (RO) of treatment entry for respondents with emotional problems was 2.6 (95% CI=1.1-6.1) versus 15.4 (95% CI=4.6-52.1) for those without antisocial behaviors. For interpersonal problems the results were similar: 2.0 (95% CI=1.0-4.0) for those with antisocial behavior versus 5.5 (95% CI=2.6-11.4) for those without antisocial behavior. There was no evidence of an interaction with health-related problems. These results indicate that both drug-related problems and antisocial behaviors increase the likelihood of entering treatment, though antisocial behaviors seems to attenuate the effect of drug-related problems on treatment entry.

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PRELIMINARY RESULTS FROM A CONTROLLED CLINICAL TRIAL OF BEHAVIOR THERAPY FOR ANTISOCIAL OPIOID ABUSERS

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Antisocial personality is commonly detected in drug abusers, where the diagnosis is associated with a poor prognosis and increased risk of HIV transmission. Here, we report preliminary results from an ongoing six month controlled clinical trial to improve treatment outcome of antisocial opioid abusers in methadone substitution therapy. Patients were randomly assigned to the Experimental (N=20) or Control (N=20) group after stratifying on baseline drug use (one month of weekly urine results), psychiatric profile (*i.e.,* presence of other comorbid diagnoses), and duration of treatment episode. The Experimental treatment incorporates a nine step contingency management approach for reducing drug use. Each step rapidly conveys greater or less control to patients over major aspects of treatment (*e.g.,* number of counseling sessions, methadone dose levels) based on urine results from the prior two weeks. The two groups were comparable on demography and baseline measures of drug use, psychiatric profile, and methadone dose. Group retention rates were similar. Primary outcome measures reported here include rates of positive weekly urine results and monthly self-reported addiction severity. Comparisons are restricted to patients who had complete data over the first 90-days. Group methadone dose levels remained almost identical over the 90-days (about 57mg). Significant outcome differences were found favoring the Experimental treatment. The Experimental group had a lower rate of urine specimens positive for any substance (25% vs. 59%), including lower rates of opioids (11% vs. 30%) and cocaine (18% vs. 36%). The Control group also self-reported an increased severity of drug use over time. Preliminary results support the viability of reducing drug use in antisocial opioid abusers with a structured behavioral intervention using positive and negative contingencies delivered in a timely manner.

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DIAGNOSIS OF PERSONALITY DISORDERS IN COCAINE-DEPENDENT INDIVIDUALS

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Personality disorders are commonly diagnosed in individuals with cocaine dependence. However, active cocaine use and withdrawal may mimic personality disorders. In order to explore this, 40 individuals entering a phamacologic treatment trial for cocaine dependence were administered the SCID for Axis II (personality disorders) at baseline and study completion (12 weeks). Cocaine use was monitored by self-report and weekly urine screens. At baseline, 68% met criteria for a personality disorder. At 12 weeks, 57% met criteria for a personality disorder. The most common Axis II diagnoses were borderline, paranoid, narcissistic and antisocial personality disorders. In comparing baseline and study termination diagnosis, 20 individuals had no change in Axis II diagnoses (NO CHANGE), six had more Axis II diagnoses (INCREASED) and 15 had less Axis II diagnoses (DECREASED). The INCREASED group had a significantly higher number of cocaine positive urine drug screens ($p \leq 0.001$) than either of the other groups (87% vs. 33% vs. 24%) and significantly more ($p \leq .001$) cocaine use by self report. In conclusion, it appears that Axis II diagnoses are common in cocaine-dependent individuals, but may be affected by cocaine use and withdrawal.

PSYCHIATRIC DIAGNOSIS IN ISRAELI OPIOID-ADDICTED METHADONE MAINTAINED PATIENTS

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In the last decade, much attention has been paid to the group of patients struggling with substance abuse and other psychiatric disorders. Research has focused on comorbidity of disorders particularly of substance abuse and depression, anxiety and/or personality disorders. This paper describes comorbidity of disorders in the opioid addicted population in a comprehensive Methadone Maintenance Clinic in Israel. The diagnoses were made on the basis of the Structured Clinical Interview for DSH-III-R on both Axis I and Axis II (SCID-I; SCID-II). The evaluation revealed that one third of the patients are diagnosed with a mood disorder and 84% are diagnosed with a personality disorder. Fourty-nine percent of patients carry the diagnosis of ASPD which is congruent with other published data. The paper addresses comparisons to other data as well as comments on the concept of "comorbidity".

HIGH STAKES: PROBLEM GAMBLING AND DRUG ABUSE

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Gambling has become more than a "coastal cities" activity. It can now be found in some form in most cities across the U.S.. The criteria for problem gambling mimic those of substance use disorders. The aims of this paper are: 1) to provide prevalence estimates of problem gambling among adults in St. Louis; 2) to explore the relationship between problem gambling and other mental health problems (especially substance dependence/abuse). The sample consists of 3.004 St. Louis Epidemiological Catchment Area (ECA) study participants, interviewed prior to the legalization of gambling in St. Louis. The Diagnostic Interview Schedule (DIS) was used to classify nongamblers (n=1543), recreational gamblers (n=1250) and problem gamblers (n=161) as well to provide rates of mental health problems for the three groups. The results show a positive and linear relationship between self-reported gambling activity and other mental health problems. Logistic regression analyses show that gamblers compared with nongamblers have an increased likelihood of having psychiatric diagnosis as well as tobacco use and dependence and alcohol use and dependence/abuse, even after adjusting for the effects of gender, race, and antisocial personality disorder. The implication is that problem gambling may be an additional "hidden" complication in treating individuals with substance use disorders. In fact, problem gamblers may be an emerging subpopulation of substance abusers requiring clinicians to modify their evaluation and treatment protocols.

ADJUNCTIVE SELEGILINE IN THE TREATMENT OF COCAINE ABUSING SCHIZOPHRENICS

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Cocaine abuse is common among schizophrenics and impairs psychosocial and treatment outcomes. Selegiline (SEL) is a "selective" MAO-type B inhibitor which indirectly elevates dopamine levels and may decrease cocaine cravings and negative symptoms of schizophrenia. This outpatient 12 week open label study compared 13 schizophrenic cocaine abusers treated with SEL (5 to 10 mg) and antipsychotic to 12 treated with desipramine (100 to 150 mg) and antipsychotic and to 15 treated with only antipsychotic (NOMED). All 40 patients were in our Dual Diagnosis Relapse Prevention Therapy (relapse prevention and social skills training). The average patient was a 30 year old, single, unemployed, black (60%) male (60%). Subjects receiving DMI had significantly better outcomes than the SEL or NOMED groups (83% of the DMI group completed the study compared to 53% of NOMED and 46% of SEL). Subjects on SEL who did better had previous substance abuse treatment. Other subtypes such as those with high negative symptoms might still benefit with SEL.

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TRIAL OF DESIPRAMINE FOR TREATMENT OF COCAINE ABUSING SCHIZOPHRENICS

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Cocaine abuse by schizophrenic patients is a serious clinical problem for which there has been little systematic study of pharmacotherapy. We administered desipraminc (DMI) or placebo in a double-blind design for 12 weeks to 80 randomly assigned male patients with cocaine abuse/dependence and schizophrenia (N = 70) or schizoaffective disorder (N = 10) (SCID-DSM III-R). Study participants were recruited from acute inpatient psychiatry units following admission for acute psychosis. Subjects were in the hospital for three weeks during which they were first stabilized on neuroleptic medication followed by initiation of study medication. Subjects were then followed weekly as outpatients up through study week 19 (study medication was administered during study weeks 1-12), and then at weeks 26, 39, and 65. All subjects received general psychosocial treatment for their schizophrenia; approximately 2/3 of subjects received group therapy targeted at their cocaine abuse (randomly distributed across the medication groups). The dose of DMI, titrated upwards with yoked adjustments, targeted steady state plasma levels between 175-250 ng/ml. DMI blood levels were performed through week 15 to monitor washout of the medication. Subjects had a urine positive for BE on admission and did not meet DSM III-R criteria for any other substance dependence disorder except nicotine. Seventy-three study participants (91% of subjects) completed two weeks of medication and 50 subjects (63%) completed the 12 week medication regimen. The medication groups differed in semiquantitative urine BE levels during study weeks 10 to 26 ($p = 0.035$, Generalized Estimating Equation method). A median of 47 patients (60% of subjects) attended the 11 clinic visits between weeks 10 and 26. For 10 of these 11 clinic visits, urine BE levels were substantially higher (3-9 fold) in the placebo group. Pairwise (Student's t test) comparisons of the medication groups demonstrated significant or nearly significant differences at study weeks 11 ($p = 0.07$), 17 ($p = 0.05$), 19 ($p = 0.06$), and week 26 ($p = 0.03$). When compared with placebo, the DMI group had 1.5 to 2 fold greater proportion of clean urines at weeks 16-19. However, there were no statistically significant differences between DMI and placebo at any given visit or across visits in proportion of clean urines, nor in study retention. These findings suggest that cocaine-abusing schizophrenic patients receiving DMI benefited from a delayed treatment effect between weeks 10 and 26, culminating at almost two months after the medication was discontinued.

DEVELOPING MEDICATION STRATEGIES AS ADJUNCTS TO TREATING PRESCRIPTION OPIATE DEPENDENCE AND COMORBIDITY

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Prescription opiates alone and in combination products (POP) (*e.g.,* codeine, hydrocodone, oxycodone) are among the most commonly used of all psychoactive agents in Canada and the United States. POP use far exceeds any approved medical indications suggesting there are substantial abuse and dependence problems with POPs. The genetically polymorphic human drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6) metabolizes these drugs to their more active metabolites. The O-demethylation and activation of POPs can be inhibited in vivo by quinidine and other inhibitors of CYP 2D6. Fluoxetine inhibits CYP 2D6 biotransformation of the prototypic substrate dextromethorphan (ki = 0.17μM and this alteration in metabolism could potentially alter the reinforcing properties of POPs and hence drug self-administmtion. We are conducting studies to characterize individuals dependent on POPs and to develop treatment strategies to assist them in discontinuing POPs when they are not needed. An initial open study in ten long-term users of POPs phenotyped and genotyped for CYP2D6, then administered fluoxetine 20 mg daily for eight weeks coupled with a structured tapering regimen, indicates that POP use decreases substantially (30 to 100% of baseline use). Depressive symptoms are common in these individuals and depressed mood scores (HAM-D, Beck Depression Inventory) also decrease with this treatment. Withdrawal symptoms as measured by the CINA were low (scores <3). The initial results of this treatment strategy will be presented including data on the impact of fluoxetine on the CYP2D6 metabolism of the POPs.

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IDENTIFYING GENETIC SUBTYPES OF SUBSTANCE ABUSE BASED ON MZ/DZ DIFFERENCES IN SYMPTOMATOLOGY

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Adoption and twin studies support genetic and environmental influences in substance abuse. However, no clear primarily genetically determined features of the substance dependence phenotype have been identified. To seek such features, we identified Diagnostic Interview Schedule (DIS) alcoholism items that showed significant MZ/DZ differences (113 male twin pairs). Scores on these "genetic" scale items were compared to scores on "environmental" items (*i.e.,* showing no significant MZ/DZ differences). Items were weighed by estimates derived from dichotomous item factor analyses. Higher genetic scale scores were associated with an earlier age of first alcohol problems ($r=-.26$, $p<=.01$) and fewer years from first intoxication to onset of alcohol problems ($r=.26$, $p<=.01$), when statistically adjusted for environmental scale scores. Higher environmental scale scores were associated with a later age of first alcohol problem ($r=.23$, $p<=.001$) and more years from first intoxication to first problem ($r=.27$, $p<=.01$), when statistically adjusted for genetic scale scores. The total number of positive items (combining both scales) was related to earlier age of first alcohol intoxication ($r=16$, $p<=.05$) but not to age of first alcohol problem nor the interval between first intoxication and first problem. These results suggest that fundamental differences in the clinical expression of alcoholism are differently related to indicators of genetic influences versus environmental influences. Findings will be discussed in terms of improving abilities to discern single-gene effects in substance abuse.

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EDUCATIONAL LEVEL AND RISK FOR ALCOHOL ABUSE AND DEPENDENCE: DIFFERENCES BY RACE-ETHNICITY

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Using prospective data, we extend and strengthen prior evidence on education and the risk of alcohol abuse and dependence among adults. Hypothesizing that risk of alcohol disorders would be greater among individuals who dropped out of high school without getting a diploma, and among those who entered college but then failed to get a degree, we examined these relationships by race-ethnicity. Data are from a total of 18,571 adult participants selected for the NIMH Epidemiologic Catchment Area Program by probability sampling of households and census tracts between 1980 and 1984. To assess occurrence of psychiatric conditions over time, staff administered the Diagnostic Interview Schedule soon after sampling and again at follow-up roughly one year later. The final sample for this report was stratified: African-American (n = 2851), and White (n = 7883). In multiple logistic regression analyses, we found that dropping out of high school was associated with elevated risk for alcohol disorders, relative to those with an AA degree or higher, among African-Americans (OR = 5.3, p = 0.0097), and Whites (OR = 3.3, P = 0.0006). In contrast, entering college but failing to get a degree was associated with a siginificantly increased risk only for Whites, but non-whiles were less numerous in the sample, causing attenuation of power. In order to assess whether this relationship was confounded by macrosocial factors of the neighborhood environment, cases were matched to non-cases by age and census tract, and conditional logistic regression analyses also were completed with simihar findings to the unconditional logistic regression analyses. If confirmed in other investigations, these findings will help to identify specific groups at high risk for alcohol disorders. Because educational level is modifiable, the results may aid in the development of prevention and early intervention programs aimed at reducing the prevalence of these disorders.

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CRAVING INTENSITY, FREQUENCY, AND DURATION AS PREDICTORS OF DRINKING

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Craving for alcohol has been hypothesized to play a major role in relapse to drinking in alcohol dependence. Craving, like any state, can vary in intensity, frequency of episodes of occurrence, and amount of time during which it is experienced. While prior studies have examined the role of internal and external cues in triggering craving, and peak intensity of craving has been used as an outcome measure in pharmacotherapy trials, the roles of frequency and duration of craving in predicting drinking in persons with alcohol dependence have not been examined.

We assessed peak craving in the prior day, total duration of craving episodes in the prior day and week, number of craving episodes in the prior day and week, whether or not craving ended in drinking, and whether or not drinking occurred in the subsequent day and week in 50 subjects. Only peak intensity of craving in the prior day was predictive of drinking, but only for the subsequent day (Spearman r=0.30, p=0.046, N=46), not the subsequent week. Peak intensity of craving was bimodally distributed. Craving episodes typically did not end in drinking (prior day: 9/81, 11%, N=49; prior week: 89/357, 25%, N=48).

These data suggest two cautions: 1) recall of craving may decay over one week, unless marked by drinking and 2) while peak craving intensity is predictive of drinking in the subsequent day, it is only weakly predictive. These data do not support the use of craving as a measure for screening potential pharmacotherapies or as a primary outcome measure in clinical trials.

EXTINCTION AND GENERALIZATION OF ALCOHOL-RELATED RESPONSES IN ALCOHOL DEPENDENT INDIVIDUALS

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The majority of alcohol dependent individuals in treatment show both autonomic and subjective responses when exposed to alcohol-related cues. This responsivity to alcohol cues has been linked to a vulnerability to relapse following treatment. The treatment method known as cue exposure has been proposed as a way in which cue responsivity can be reduced thereby decreasing the risk of relapse. The processes involved in cue exposure can be explained in terms of the classical conditioning concept of extinction *i.e.,* individuals are repeatedly presented with alcohol-related cues without the associated intake of alcohol. In the present study fifty male alcohol dependent individuals participated in a controlled test of extinction. Subjects were randomly assigned to either an experimental or control group. The experimental group were presented with ten exposure trials of the sight and smell of alcohol whilst the control group were presented with a neutral beverage. A test of the robustness of the extinction trial was conducted following the completion of the extinction sessions. Subjects were presented with the alcohol cue in a different room in order to examine whether the extinguished responses generalised to a different environment. Repeated measures MANOVA showed that only those subjects who were repeatedly presented with the alcohol cue showed a significant reduction in cue-elicited swallowing, skin conductance level and craving for alcohol. MANOVA indicated that extinguished responses remained diminished in magnty can be reduced thereby decreasing the risk of relapse. The processes involved in cue exposure can be explained in terms of the classical conditioning concept of extinction *i.e.,* individuals are repeatedly presented with alcohol-related cues without the associated intake of alcohol. In the present study fifty male alcohol dependent individuals participated in a controlled test of extinction. Subjects were randomly assigned lo either an experimental or control group. The experimental group were presented with ten exposure trials of the sight and smell of alcohol whilst the control group were presented with a neutral beverage. A test of the robustness of the extinction trial was conducted following the completion of the extinction sessions. Subjects were presented with the alcohol cue in a different room in order to examine whether the extinguished responses generalised to a different environment.

BEHAVIORAL RESPONSES TO ETHANOL IN SOCIAL DRINKERS FOLLOWING NALTREXONE PRETREATMENT

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Recent studies suggest that activation of the endogenous opioid system may underlie some of the effects of ethanol (EtOH). For example, EtOH stimulates the release of endogenous opioids in laboratory animals and humans. Further, the opioid antagonist, naltrexone (NTX), decreases EtOH consumption in laboratory animals and decreases relapse rates in alcoholics. However, we recently reported that in normal social drinkers, NTX did not alter the subjective effects (*e.g.,* ratings of euphoria, drug liking) of a moderate dose of EtOH (0.5 g/kg). The present study further examined the effects of NTX on acute responses to EtOH by testing a lower dose of EtOH and by examining responses in both light and moderate drinkers. To date, 18 (of 25 total) males and females have participated in a double-blind, placebo-controlled study in which they consumed an EtOH (0.25 g/kg) or placebo beverage after NTX (0,25 or 50 mg) pretreatment. Subjects completed standardized mood and subjective effects questionnaires during the session. EtOH produced its prototypic effects including increased ratings of “feel drug” and “feel intoxicated” and increased sedative-like effects. NTX did not significantly modify the subjective effects of EtOH and did not differentially affect responses to EtOH in light (n=10) and moderate (n=8) drinkers. These findings are consistent with our previous report that NTX did not attenuate the subjective effects of EtOH in social drinkers. However, these findings contrast with reports suggesting that activation of the endogenous opioid system underlies some effects of EtOH. It may be that the effect of NTX depends on the subject population tested (*i.e.,* alcoholics versus social drinkers) or that separate mechanisms mediate subjective effects and consumption.

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TREATMENT OF ALCOHOL DEPENDENCE WITH NALTREXONE BY PRIMARY CARE PROVIDERS

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Naltrexone has been demonstrated to be effective in reducing alcohol consumption and relapse when administered in combination with traditional psychotherapy in patients who are alcohol dependent. To address the question of treatment intensity, we evaluated naltrexone administered in conjunction with a therapeutic approach of advice and clinical management administered by primary care providers to alcohol dependent individuals. To date 29 patients have completed the ten week study. Their mean age was 45 years, 83% (24/29) were male, 79% (23/29) were employed, and they reported a mean of 1.1 prior substance abuse treatment episodes. Of this group, 66% (19/29) successfully completed treatment, 14% (4/29) were discharged because of protocol violations or adverse drug effects, and 2 1% (6/29) withdrew from the study. Self help meetings were attended by 31% (9/29) of patients. Of the patients who successfully completed the study, 63% (12/19) were felt to be moderately or very much improved in terms of their alcohol dependence and 79% (15/19) continued therapy with their primary care provider. In conclusion, treatment of alcohol dependence with naltrexone by primary care providers appears to be both feasible and effective.

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THE EFFICACY AND SAFETY OF ACAMPROSATE ON THE MAINTENANCE OF ABSTINENCE IN WEANED ALCOHOLICS

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A double-blind multicentric study was carried out IO evaluate the effectiveness of Acamprosate as an aid in the maintenance of abstinence in weaned alcoholics (diagnosed as DSM-III alcoho1 Dependence Syndrome) after the acute withdrawal phase. Eighteen centers for the treatment of alcoholism, scattered throughout the Italian Regions (North, Middle and South) were enrolled for the study. A total of 340 patients were screened and 330 were randomized in order to enter a 180-day treatment with Acamprosate (164 patients) or placebo (166 patients). A follow-up period of 90 days after the discharge from treatment was carried out in both groups. In order to evaluate the efficacy of the treatment, the abstinence period by visit, the cumulative abstinence duration (CAD) and the survival in abstinence were the considered variables. The statistical analyses applied were: attendance-relapse-abstinence proportion, intention to treatment success-failure proportion, survival analysis of the time to first relapse, and multifactorial, mulliple regression, non-parametric correlation analyses of variables related to CAD. During the entire period of treatment Acamprosate (2gr/day) was more consistently effective than placebo in maintaining abstinence in alcoholic patients. The abstinence rate was 30% higher and the CAD was significantly longer in the active drug-treated group than in placebo-treated subjects. Acamprosate was well tolerated. The data demonstrate that the interaction between the setting of an outpatient program and the pharmacological therapy is an important issue in the prevention of relapse in alcoholics in the short-time period after detoxification.

PSYCHIATRIC DIAGNOSES AND TREATMENT OUTCOME IN METHADONE MAINTAINED PATIENTS

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Introduction. A number of studies with treated opiate addicts have examined the relationship of Axis I or Axis II psychopathology to outcome. There are, however, no empirical reports which have considered the diagnostic information from both Axis I and II together to examine treatment outcome. Subjects and Methods. The subjects were 220 men recently admitted to methadone maintenance. All received a baseline Addiction Severity Index (ASI) to assess substance use and psychosocial functioning, as well as a structured diagnostic interview to determine DSM-III-R Axis I and II disorders. Ninety-one percent of the subjects (n=200) were evaluated seven months later with a follow-up ASI. Results. Subjects with both a current (nonsubstance use) Axis I disorder and a personality disorder had the worst outcomes and subjects with neither had the best outcomes. Those with either a current Axis I disorder&r a personality disorder had intermediate outcomes. Psychiatric severity as measured by the ASI psychiatric composite score or interviewer severity rating identified subjects with worse outcomes as well as diagnoses did.

THE FIRST COMPREHENSIVE METHADONE MAINTENANCE TREATMENT AND RESEARCH CLINIC IN TEL AVIV, ISRAEL: PSYCHOSOCIAL FINDINGS

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This paper describes the preliminary psychosocial findings collected at a new model Methadone Maintenance Treatment program in Tel Aviv, Israel, established following earlier experience in the U.S.A.. We have hypothesized that similar psychosocial disorders may be shown in drug addicts in Israel, and improve while in treatment, in a model clinic patterened after a most effective clinic in the U.S.A.. The Adelson Clinic was established in a large Tel Aviv University Medical School affiliated hospital. Patients are treated with methadone combined with psychosocial treatment provided by a multi-disciplinary team. The Clinic has also set specific research plans. Patients in Methadone Maintenance treatment have been carefully studied in order to determine the psychosocial factors. The similarities and differences among patients were analyzed and understood in order to develop a fully comprehensive paradigm for the treatment of addiction. Biographical data was collected as well as data on addiction history (using the Addiction Severity Index - ASI) psychiatric sympotomology (using the Symptom Checklist 90 - Revised - SCL-90-R) and mood states (using the Profile of Mood States - POMS). Eighty percent of the patients have psychiatric comorbidity of addiction disorder and other psychiatric disorders as has been reported in studies of patients in the U.S.A.. Periodical assessments show reduction in severity of substance abuse, psychiatric symptomology and stabilization of mood states. We concluded that the same psychosocial disorders are shown in the Israeli drug addict population, and an improvement is seen while in a methadone maintenance treatment and research clinic patterned in Israel after a very effective clinic in the U.S.A..

VIOLENCE, PSYCHIATRIC COMORBIDITY AND GENDER: PREDICTORS OF OUTCOME IN METHADONE PATIENTS

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We examined gender differences in the frequency of violence, posttraumatic stress (PTSD) and depressive (DD) disorders in methadone patients, and their associations to treatment outcome. METHOD: 96 (49 women, 47 men) consecutively-admitted inner-city opiate abusers presenting for methadone treatment were evaluated by experienced diagnosticians for histories of childhood physical and sexual abuse (CPSA), adulthood exposures to violent trauma (ADVIOL), PTSD and DD with a modified SCID (SAC-version). Weekly urine drug screens assessed ongoing polydrug abuse. Three month drop out rates were also determined. RESULTS: Men with CPSA had higher rates of PISD than those without (Chi-Sq=10.0; p<.001). Women with CPSA or ADVIOL had higher rates of PTSD (Chi-Sq=15.0, p<.001; Chi-Sq=6.1, p<.01), and DD (Chi-Sq=11.8, p<.001; Chi-Sq=10.5, p<.001). 2 X 2 ANOVAs for rates of cocaine abuse during treatment revealed main effects for PTSD (F=6.8; p<.01) and an interaction effect for DD by sex (F=13.6; p<.001). Histories of CPSA for both sexes also predicted higher rates of cocaine abuse (F=4.9; p<.05). An ANCOVA on polydrug abuse (factors: PTSD, DD, gender, and polydrug use on admission) revealed significant main effects for PTSD and DD and interaction effects for PTSD by sex and PTSD by DD (Overall F=5.8, p<.001). PTSD and DD did not predict drop-out rates. In 71 .1% of cases, exposure to trauma preceded the onset of drug abuse. CONCLUSION: High rates of CPSA, PTSD and DD were associated with poorer treatment compliance (*i.e.,* ongoing polydrug abuse) for both sexes. DD may be a poorer prognostic indicator for men than for women. ADVIOL was associated with more psychiatric problems for women than for men. Findings confirm the need for routine assessment and treatment of violence and PTSD for both sexes. Implications for treatment are discussed.

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PSYCHOACTIVE SUBSTANCE USE DISORDERS IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Background: We evaluated the association between attention deficit hyperactivity disorder (ADHD) and the psychoactive substance use disorders (PSUD) in adults with ADHD attending to issues of comorbidity with mood, anxiety, and antisocial disorders. We hypothesized that psychiatric comorbidity would be a risk factor for PSUD. Methods: We compared findings in 120 referred adults with a clinical diagnosis of childhood-onset ADHD with those of a sample of non-ADHD adult controls (N=248). All childhood and adult diagnoses were obtained by structured psychiatric interviews for DSM III-R. Results: There was a signiticantly higher lifetime risk for PSUD in ADHD adults than in controls (52% vs 27%; p<0.1 Although ADHD and control subjects did not differ in the rate of alcohol use disorders, ADHD adults had significantly higher rates of drug and drug plus alcohol use disorders than controls. ADHD conferred a significantly increased risk for PSUD independently of comorbidity. Antisocial disorders conferred a significantly increased risk for PSUD independently of ADHD status. Mood and anxiety disorders increased the risk for PSUD in both ADHD and control subjects, but more demonstrably in controls. Conclusions: Although comorbidity increases the risk for PSUD in ADHD individuals, ADHD by itself was a significant risk for PSUD in ADHD adults.

ROLE OF ANTISOCIAL PERSONALITY AND DEPRESSION IN CLIENT RETENTION IN COMMUNITY-BASED DRUG ABUSE TREATMENT PROGRAMS

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This study examines the effects of antisocial personality (ASP) disorders and major depressive episodes on client retention in communily-based methadone, outpatient drug-free, and long-term residential treatment programs. The data came from the Drug Abuse Treatment Outcome Study, a large longitudinal study funded by the National Institute on Drug Abuse of clients entering treatment in the early 1990s. Each modality contains a relatively large number of representative programs (*i.e.,* 20 to 30) with a corresponding total sample size within each modality of roughly 2,000. The general analytic strategy was to model the probability of remaining in treatment at least three months as a function of variables known or hypothesized to be related to retention along with an indicator of an ASP diagnosis and an indicator of a lifetime depression diagnosis. Logistic models were estimated separately for females and males within each modality. The major findings involved the strong interaction between ASP and heavy alcohol use for male methadone clients and the strong interaction between depressive episodes and regular cocaine use for female methadone clients. For males, the negative effect of ASP on retention was much stronger for heavy alcohol users than for nonheavy alcohol users. For females, the effect of depressive episodes on retention was strongly positive for nonregular cocaine users and slightly negative for regular cocaine users. In summary, ASP plays an interactive role in affecting retention for males, and depression plays an interactive role in affecting retention for females. However, the interactions were only strong within the methadone modality.

THE COMORBIDITY OF DSM-III-R DRUG DEPENDENCE WITH OTHER PSYCHIATRIC DISORDERS IN THE NATIONAL COMORBIDITY SURVEY

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Data from the National Comorbidity Survey (NCS), a nationally representative general population epidemiologic survey of respondents ages 15 to 54 (N=8098), show that lifetime and 12-month associations (odd-ratios) of DSM-III-R mental disorders with DSM-III-R drug dependence are all positive, largely statistically significant among both men and women, and rarely significantly different between the sexes. Men are significantly more likely than women to report temporally primary drug dependence (9.2% vs. 3.9%). although the vast majority (80%) of both men and women with a lifetime drug disorder report that at least one mental disorder occurred at an earlier age than their first drug use disorder. The distribution of the primary disorders that are associated with secondary drug dependence differ by sex; among the drug dependent, women are more likely than men to have a primary anxiety (68.7% vs. 36.3%) or affective disorder (17.9% vs. 6.7%), and less likely to have a primary alcohol (7.7% vs. 23.6%) or behavior-related disorder (13.3% vs. 40.7%). Average time to dependence is signiticantly longer for women than men when the primary disorder is social phobia (10.6 vs. 8.1 years), mania (15.8 vs. 5.3 years), or alcohol abuse (6.9 vs. 2.5 years). The evidence concerning the high proportion of cases in which mental disorders are primary lifetime conditions suggests that interventions aimed at the primary prevention of secondary disorders are an important focus for future research.

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POST-TRAUMATIC STRESS DISORDER AMONG DRUG USERS: IS IT A REAL DISORDER?

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Several studies have recently found a strong association between Post-Traumatic Stress Disorder (PTSD) and substance use disorders. In a sample of substance users both in and out of treatment, we have been able to examine the characteristics of PTSD by gender, type of substance use reported, and other comorbid psychiatric disorders. From a sample of 464 substance users in the St. Louis ERSA study, (a NIDA-funded study of the effect of treatment on HIV risk behaviors) we found that women were more likely than men to be exposed to a traumatic event, that is, a PTSD-qualifying event (40% vs. 30%), and were more likely to meet criteria for PTSD once exposed (30% vs. 15%). We also found that exposure to a qualifying event was associated with the use of both cocaine and opiates, IDU, Adult Antisocial Behavior, Depressive and Anxiety disorders. Meeting criteria for the full PTSD syndrome, however, was predicted by only Anxiety and Phobic Disorders. In addition, the age of onset of substance use preceded the age of onset of exposure to the traumatic event. How these findings compare with others' results will be discussed, as will the implications for the new DSM-IV criteria for PTSD on future studies of these comorbid conditions.

LINEARITY OF SERUM NICOTINE CONCENTRATION AND SUCCESS OF NICOTINE PATCHTHERAPY IN TOBACCO DEPENDENCY TREATMENT

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Hypothesis: *Success in stopping smoking with nicotine patch treatment (NPT) would be directly and linearly proportional to the serum nicotine concentration ([SeNic]) produced by NPT ([SeNic]$_{NPT}$).* (Since smokers self-regulate nicotine intake when using tobacco cigarettes (cigs), we expressed [SeNic]$_{NPT}$ as a function of [SeNic] during baseline, while smoking cigs before NPT began ([SeNic]cigs) - % replacement (% repl). Finally, because of nicotine's short T1/2 (~ 2 hours), our primary measurement was nicotine's major metabolite, cotinine (Cot), with a T1/2 ≈ 20 hours.) Until our study, this hypothesis has never been tested. Eighty-four men and women were assigned in prospective, randomized, double-blind, placebo-controlled fashion to receive 0% (placebo), 50%, or 100% nic rep1 during treatment (Rx). using 3.30 cm^2 NPs daily (qd), delivering up to 45 mg nic/16 hours for six weeks after Target Quit Date (TQD), preceded by a ten day dose titration phase, followed by six week tapering (Tap) phase + three month follow-up (FU) phase off NP. Total study duration was six months. Double-blind was strictly maintained throughout the entire study. The observed data confirmed our hypothesis, not only at each measurement (meas) during NPT, but also at each meas during the NPT tapering + 3 mo FU. E.g., continuous nonsmoking rates (objectively validated by CO ≤ 9ppm) were, six weeks after TQD, 42%, 44%, 65%, and 82% for 0, >0 to <50, ≥ 50 to <100, and ≥ 100 % rep1 actually achieved (Mann-Whitney $p<0.0138$), and six months after TQD, for the same % rep1 levels, 9%, 16%, 21% and 25% (Mann-Whitney $p<0.2124$). These data also showed no plateauing of the SeNic Concentration - Response Curve at any time. Side effects were minimal and of no clinical consequence. Continuous nonsmoking rates during Rx, Tap, and FU with NP are directly and linearly proportional to [SeNic] actually achieved during the Rx phase. Also, currently suggested "maximum" NP doses (15 mg nic/16 hours or 22 mg nic/24 hours) are woefully inadequate for a substantial proportion of smokers being treated with NP.

THE EFFICACY OF NORTRIPTYLINE AS AN ADJUNCT TO PSYCHOLOGICAL TREATMENT FOR SMOKERS WITH AND WITHOUT DEPRESSIVE HISTORIES

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The present study examined the efficacy of nortriptyline and two psychological group treatments for nicotine dependence in persons with a history of major depressive disorder (MDD). Preliminary findings are based on 119 subjects; 47.8% female, 35% reported a history of MDD. Mean age = 39.4 years. Mean daily cigarettes = 22.2. Mean years smoking = 20.4. Subjects were randomly assigned to one of four experimental cells in a 2 X 2 design: cognitive-behavioral mood-management intervention (10 sessions) versus standard health-education treatment (five sessions) X nortriptyline versus placebo. Here, we report preliminary results for the nortriptyline arm of the study. Nortriptyline treatment took place during weeks 1-12. Psychological treatment began at week four, and continued for eight weeks. Nortriptyline dose began at 50 mg for all subjects. Serum levels were assessed at weeks 2, 4, and 6 to titrate dosage. Target therapeutic serum levels were based on recommendations for the treatment of depression, 50 to 150 ng/ml. The final dosage was usually between 75 and 100 mg. There were seven assessments: baseline, pre-group treatment, (week four), week eight, posttreatment (week 12) and weeks 24, 38, and 64. At each assessment, self-report, and biochemical data on cigarette use were collected. Hierarchical analyses indicate a positive effect for nortriptyline at week eight (54% of subjects on active medication were abstinent vs. 35% on placebo, $p < .05$), and week 12 (52% vs. 35%. $p < .05$), independent of MDD history. Preliminary findings indicate that nortriplyline may be effective as an adjunct to treatment regardless of depression history. If final analyses support these preliminary findings, smokers who want or need a pharmacological treatment may have an option not currently available to them.

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CONCURRENT AGONIST/ANTAGONIST EFFECTS ON SMOKING BEHAVIOR AND REWARD

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Eighty cigarette smokers were studied during four weeks of *ad lib* smoking, during which they received nicotine and/or mecamylamine in a 2x2 factorial design. Nicotine was administered with skin patches delivering 21 mg/24 hours and mecamylamine was administered in capsules (5 mg twice per day). Smoking behavior was assessed by self-reports of cigarettes smoked each day, expired air carbon monoxide, and plasma nicotine and cotinine concentrations. Subjective smoking satisfaction and craving for cigarettes were assessed weekly. Nicotine and mecamyhamine had significant independent effects in reducing *ad lib* smoking behavior; combined administration markedly suppressed smoking to approximately 50% of baseline levels. Smoking satisfaction was attenuated by mecamylamine, with a trend for greater attenuation by the nicotine/mecamylamine combination. An interactive effect of nicotine and mecamylamine was observed in reducing craving for cigarettes; neither drug alone affected craving but the combination significantly reduced craving. These results support the hypothesis that the therapeutic effects of an agonist and antagonist do not necessarily cancel in terms of reducing substance abuse and blocking drug reward; instead, a synergistic effect may be obtained.

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TEST OF A RELAPSE PREVENTION STRATEGY FOR SMOKING CESSATION: COMBINED NICOTINE PATCH AND GUM

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The purpose of this study was to assess the efficacy of combined nicotine patch and nicotine gum in a relapse prevention model. Sixty five adult smokers were maintained on 24-hour nicotine patches in conjunction with a ten week counseling program. Subjects were also randomly assigned to one of three relapse prevention conditions: 2 mg nicotine gum, placebo gum, or no gum. All subjects were instructed to monitor high risk situations and to develop relapse prevention skills. Subjects in the gum conditions were instructed to use the study gum to cope with smoking urges, while subjects in the no gum conditions were instructed to use other behavioral coping methods. At 12-weeks, overall results indicated that combined patch and gum produced the highest cotinine levels, but failed to slow relapse rates compared to patch with placebo gum or with no gum. Results also supported previous observations that any smoking early in treatment predicts subsequent relapse. Further analyses revealed that for those who smoked within the first two weeks of treatment, the addition of active gum had no beneficial effect on relapse outcomes. However, in the early abstainers, a relapse prevention effect of active vs. placebo gum in the predicted direction suggested that the long-term relapse prevention utility of patch plus active gum may be more appropriate for those quitters who can maintain early abstinence. Future research using this model should consider sub-group differences between early smokers and abstainers, issues of compliance and medication use patterns, and the potential relapse prevention utility of other nicotine replacement products such as 4 mg nicotine gum, nicotine aerosol sprays, and nicotine inhalers.

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SUBSTANCE ABUSERS' SMOKING CESSATION FOLLOWING ADVICE

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This report details the preliminary outcome in the first 75 subjects who completed the advice session in a randomized trial investigating whether alcoholics/drug addicts enrolled in outpatient substance abuse treatment will stop smoking when advised by a physician to quit (Standard), and whether quit rates increase when that advice is linked to adverse health effects from smoking (Linked). Subjects were male veterans who tended to be single (85%) unemployed (56%), African American (44%) or Caucasian (43%) 46.8 years old, and have 13.3 years of education. Primary drug of abuse was alcohol (34%, cocaine/crack (29%) or heroin (24%). At baseline, cigarettes averaged 21/day, and mean CO level was 24. No demographic or smoking measure differences were found between the two conditions. One-month after the advice session, no subject had quit smoking. However, self-reports indicated a small treatment group difference in whether subjects had reduced the number of cigarettes smoked (68% of the Linked group had "cut down" vs. 43% of the Standard group, p=.043), but no corresponding difference was found in CO levels. These results suggest that advice to stop smoking may be less effective in this patient population, and self-report of smoking status without biological verification in smoking cessation studies must be questioned.

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CONTINGENCY MANAGEMENT FOR SMOKING CESSATION AMONG METHADONE MAINTAINED ADDICTS: A PILOT STUDY

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This project evaluated: (1) feasibility of contingency management (CM) for smoking cessation in methadone maintained addicts; and (2) possible associations between smoking cessation and illicit drug use. CM procedure provided incentives in the form of vouchers that could be exchanged for merchandise for "no smoking" breath samples (CO levels <= 4 ppm). The initial voucher was worth $2.50 and consecutive vouchers indicating continued smoking abstinence increased $.50 in value. Breath and urine samples were collected three times per week, but contingencies were for breath samples only. Urine samples were collected and analyzed to detect cocaine and opiate use using the Treatment Effectiveness Score (TES; Ling, *et. al.,* 1994), which assigns one point for each scheduled clean urine. Seventeen methadone maintained cigarette smokers received four weeks of CM. CM patients significantly reduced breath CO levels from baseline (Mco baseline = 16.0 ppm) to end of treatment (Mco end = 10.35 ppm). Nine patients (52.9%) provided at least one "no smoking" sample ("any response"); seven (40.8%) produced at least two consecutive "no smoking" samples ("minor response" - three days of smoking abstinence); and four patients (23.4%) maintained one week or more of smoking abstinence ("major response"). TES analyses indicated a link between smoking abstinence and reduced cocaine use, though not reduced opiate use. Patients with "minor" or "major" response to CM treatment had median cocaine TES scores twice those modest support for CM as a stop smoking technique among this population, and raised questions about possible shared biological and psychological mechanisms for tobacco and cocaine use.

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A COMPARISON OF REINFORCEMENT PROCEDURES FOR PROMOTING ABSTINENCE IN CIGARETTE SMOKERS

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This ongoing study compares the efficacy of several contingency-management strategies for promoting smoking cessation. Sixty smokers who were not trying to quit smoking and who exhibited an initial CO reading of > 18 ppm were assigned to one of three groups. Subjects in all three groups were asked to refrain from smoking for one week. Subjects provided three CO samples daily. CO readings that were < 11 ppm were considered to represent abstinence. Group 1 subjects received payment contingent on presenting with CO readings indicating abstinence. The magnitude of payment escalared for consecutive abstinence by $0.50 increments from an initial value of $3.00. Additionally every three consecutive CO readings indicating abstinence were followed with a $10.00 bonus. If a subject presented with a CO reading indicating smoking they were reset back to the initial $3.00 value. Subjects in Group 2 were paid a fixed amount ($9.80) every time they provided a CO reading which indicated abstinence. This maintained the magnitude of reinforcement consistent with that used in Group 1 but presented it in a nonescalating fashion and without the bonuses. Group 3 served as a noncontingent control group whose schedule of reinforcement was yoked to Group 1. All subjects received $50.00 upon completion of the study. Preliminary results from Group 1 appear promising. All subjects have been able to reduce their smoking and some remained abstinent for the entire week. Results from the comparison groups are not yet available. These results may be important because they appear to represent a very practical mechanism to induce abstinence in cigarette smokers and other types of drug users. This study will be completed this spring.

PAST HISTORY OF ALCOHOL PROBLEMS AND THE ABILITY TO STOP SMOKING

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As part of a clinical trial of transdermal nicotine (TN), smokers completed the Short Alcohol Dependence Data (SADD) questionnaire. The 13 sites randomized 1040 heavy smokers to 0, 21, 35 or 44 mg doses of TN plus group behavior therapy. Subjects with a current SADD > 9 were excluded. Assignment lo drug doses has not been broken; however, data are available from 157 subjects from the VT and MN sites. Fourteen percent of subjects had a past SADD score of > 9 indicating previous significant alcohol problems. Forty-six percent had a current SADD score of 1-9 suggesting some alcohol problems in the last year. Subjects with higher past or current SADD scores did not have higher Fagerstrom Nicotine Dependence scores, shorter times to first cigarette or less cessation, although there was a nonsignificant trend for those with a higher past SADD to be less likely to continuously abstain through six months (0% vs 17%, p = .07). When 12 month data are collected, we will use. data from all sites to better test the above issues and to test our prior finding that nicotine replacement is especially helpful to smokers with a history of alcohol problems (J Subs Abuse Tx 10:181, 1993).

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PREVENTION OF SMOKING RELAPSE IN CARDIAC PATIENTS: INITIAL FINDINGS

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The health benefits of maintaining smoking abstinence following a major cardiac event are unequivocal and well-documented. Although rates of quitting in chronic smokers subsequent to the diagnosis of acute myocardial infarction (MI) are high, the pattern of relapse after initial cessation is surprising similar to that seen in healthy smokers and in other addictions. We have been evaluating the effectiveness of a smoking treatment intervention to prevent relapse among post-MI patients. Thirty-six patients seeking treatment for smoking cessation were randomly assigned to an individually behaviorally-based Relapse Prevention (RP) treatment or Brief Counseling (BC), consisting of brief advice and written material on smoking cessation. Another group of 36 patients who refused treatment assistance, preferring lo quit on their own, comprised a third condition called "self-quitters" (SQ). Treatment refusers, or SQ subjects, were more likely to be male, have longer past abstinence periods, lower levels of nicotine dependence, and perceive smoking as having less impact on their cardiac condition. After three months, validated abstinence rates were 76% for RP patients, 42% for UC patients, and 47% for SQ patients, p<.0.5. Validated abstinence rates at later follow-up intervals (6-, 9-, and 12-month) were not significantly different for RP, BC, and SQ groups. Of the total sample, 35% of subjects were abstinent over the entire 12-month follow-up. Nonabstinent patients who received RP treatment had significantly lower smoking rates than patients who received BC. Logistic regression analyses showed that baseline self-efficacy and depression scores predicted one year smoking status aud thus may be important treatment considerations in future research on smoking cessation in patients with smoking-related medical risks.

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PERSONALITY DIFFERENCES RELATED TO SMOKING AND ADULT ADHD

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We previously reported that adult ADHD patients smoke at nearly twice the rate observed in the general population. Personality factors related to this phenomenon, however, have yet to be described. The present study compared Tridimensional Personality Questionnaire (TPQ) scores received by three subject groups: (1) Current smokers diagnosed with adult ADHD (ADHDSmk, n=14); (2) Current smokers without adult ADHD (NonADHDSmk, n=22); and (3) Adult ADHD patients who had never been regular smokers (ADHDNevSmk, n=17). The scores of these groups were also contrasted with previously established TPQ normative data. All Ss were White males with a mean age of 30.2±8.3 and 15.0±3.3 years of education. There were no group differences in age or education. ADHDSmk Ss started smoking at a significantly younger age than NonADHDSmk Ss (14.8±2.8 vs 17.3±3.2 years, $p<.05$). On the Novelty Seeking (NS) dimension of the TPQ, all groups scored more than a standard deviation above the norm, and ADHDSmk Ss scored significantly higher than NonADHDSmk Ss. On the Harm Avoidance dimension (HA), only the ADHDNevSmk Ss scored more than one standard deviation above the norm. On the Reward Dependence (RD) dimension, groups were not elevated relative to norms; on the RD subscale assessing Dependence, however, ADHDNevSmk Ss scored significantly higher than ADHDSmk Ss. The earlier onset of smoking in ADHD adults suggests that early smoking prevention efforts may be particularly important for ADHD children. Dependence subscale results suggest that nonsmoking ADHD Ss may derive greater reinforcement from social/ interpersonal factors than their smoking counterparts. Previous studies have reported that both smokers and ADHD patients have elevated NS scores; the present study suggests an additive effect for smokers with ADHD. Obversely, this exaggerated tendency towards thrill-seeking in ADHDSmk Ss may complicate smoking-cessation treatment in this population, since the health consequences of smoking may be of less concern to ADHD Ss.

ORAL COCAINE IS PREFERRED TO LIDOCAINE UNDER A SCHEDULE-INDUCED DRUG SOLUTION SELF-ADMINISTRATION CONDITION

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Using the method of schedule-induced oral drug solution self-administration in three hours daily sessions, rats preferred cocaine (COC) solution (0.24 mg/ml) to vehicle (water) after cocaine had first been made up with a tastant vehicle (1.5% glucose and 0.08% sodium saccharin), with this vehicle concentration gradually reduced to zero (water vehicle). The session left-right COC-water position was a quasirandom sequence. Then, the rats were divided into two groups. One continued to receive the COC-water choice, and the other was rapidly faded into a choice between (0.19 mg/ml) lidocaine (LIDO) and water. Both groups continued to prefer drug solution to water. Next, when given a choice between these isomolar solutions, cocaine was chosen almost exclusively. To determine if this preference was merely due to a gustatory preference difference, COC concentration was slowly increased step-wise to 0.68 mg/ml, while LIDO was held constant. COC remained almost exclusively preferred, and daily intakes were approximately 62 mg/kg. These results indicate that oral COC may come to function either as a gustatory SD or as a reinforcer, or both.

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INTERACTIONS AMONG LAAM, NALTREXONE AND MORPHINE: EFFECTS ON SCHEDULE-CONTROLLED BEHAVIOR IN PIGEONS

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The μ opioid 1-α·-acetylmethadol (LAAM) has a long duration of action and is currently being evaluated for its utility in treating opioid dependence. This study examined the acute effects of LAAM in pigeons responding under a FR20 schedule of food presentation. LAAM decreased response rates with a dose of 5.6 mg/kg decreasing rates to 10% of control four hours after injection; response rates returned to control levels by 14 hours after LAAM. Naltrexone dose-effect curves were shifted 100-fold to the left 1 and 24 hours after 5.6 mg/kg of LAAM; there was no changc in naltrexone dose-effect curves seven days after 5.6 mg/kg of LAAM. Morphine dose-effect curves were shifted only 2- to 3-fold to the right 24 hours after 5.6 mg/kg of LAAM. increased sensitivity to naltrexone the day after LAAM administration indicates acute dependence developed to LAAM and further suggests that repeated, perhaps relatively infrequent, exposure to LAAM is likely to produce robust physical dependence similar to that produced by chronic exposure to other μ opioids.

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DISCRIMINATIVE STIMULUS EFFECTS OF BUTORPHANOL: INVOLVEMENT OF MU, KAPPA AND DELTA OPIOID RECEPTOR ACTIVITY

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Separate groups of pigeons were trained to discriminate a low (0.1 mg/kg). medium (1.0 mg/kg) or high (5.6 mg/kg) dose of butorphanol from saline using a standard, two-key, food-reinforced, drug discrimination procedure. The stimulus effects of butorphaonol were reversed by a low dose (0.1 mg/kg) of naloxone and a high dose (10 mg/kg) of naltrindole. In each of the training dose groups, opioids with low (*e.g.,* nalbuphine, nalorphine, levallorphan), intermediate (*e.g.,* butorphanol, buprenorphine, (-)-pentazocine) and high (*e.g.,* 1-methadone, fentanyl) efficacy at the mu receptor produced high levels of drug-appropriate responding. Based on their ED50 values, each of these opioids was most potent in the low dose group and least potent in the high dose group. In the low dose group, various kappa opioids (*e.g.,* spiradoline, bremazocine, U69,593) produced intermediate levels of drug-appropriate responding, whereas in the medium and high dose groups these kappa opioids produced primarily saline-appropriate responding. Finally, the delta opioid BW373U86 produced high levels of drug-appropriate responding in the low dose group and intermediate levels in the medium and high dose groups; these effects were reversed by a low dose of naltrindole (1.0 mg/kg). In contrast to the substitution patterns produced by mu, kappa and delta opioids, sigma/PCP compounds (*e.g.,* [+]-NANM, [+]-cyclazocine) produced primarily saline-appropriate responding in each of the training dose groups. The current findings suggest that mu, kappa and delta opioids share similar stimulus effects with low training doses of butorphanol, whereas only mu opioids share stimulus effects with medium and high training doses of butorphanol.

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I.V. SELF-ADMINISTRATION BEHAVIOR IN INBRED MICE

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Molecular genetic strategies are currently being used to alter the neurobiology of the mouse brain. An important task of the molecular biologist, behavior pharmacologist, and behavior geneticist must be to assess the consequence and relevance of these changes on behavior. The purpose of this study was investigate the ability of inbred mice with known variations in opiate receptor concentration to acquire i.v. morphine self-administration behavior under two schedules of reinforcement: Fixed Ratio 4 (FR4) and Mixed Variable Interval 30' extinction (V130' extinction). Four inbred strains were used in this study; the p-opiate deficient CXBK/ByJ (BK), opiate rich CXBH/ByJ (BH), C57BL/6J, and BALB/ByJ mice. Mice used in the FR4 experiment were initially trained for water reinforcement, surgically implanted with an i.v. catheter, allowed three days to recover, then given access to 1.0, 0.3, 0.1, and 0 mg/kg/inj morphine. Mice used in the mixed schedule were cathererized, allowed to recover, then placed in the chamber for at least nine days with 1.0 mg/kg/inj available. The mixed schedule was used in order to examine drug-seeking behavior under conditions with equivalent total drug-intake. Self-administration behavior was dose-dependent across all strains. The BK mice and BH mice took the most and least amounts of drug, respectively, across all doses under the FR4 schedule of reinforcement. In addition, the BK and BH mice emitted the most and least amounts of behavior, respectively, under the VI30' extinction schedule of reinforcement. These data demonstrate the capacity for inbred mice to self-administer drug under tow schedules of reinforcement and demonstrate a significant effect of genotype on drug-seeking behavior that was influenced by opiate receptor concentration.

INTRACRANIAL SELF-STIMULATION (ICSS): SENSITIZATION TO AN OPIOID ANTAGONIST FOLLOWING ACUTE AGONIST PRETREATMENT IN RATS

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Acute mu-opioid agonist pretreatment (four hours) dose-dependently sensitizes rats responding for food reinforcement to the rate-decreasing effects of naltrexone (NTX). The present study was performed to determine if acute agonist-induced sensitization occurs in an ICSS paradigm. Eight adult male Sprague-Dawley rats were trained to respond in an autotitration procedure. Every response on a "stimulation" lever resulted in the delivery of a 250 msec train of constant current stimulation to the medial forebrain bundle, and every 15th response decreased the frequency of pulses within each stimulation train by 5 Hz. At any time, a response on a second "reset" lever restored the frequency available on the stimulation lever to its starting level (100 Hz). Training and once-weekly testing occurred in daily sessions consisting of live 15 minute trials, each preceeded by a 15 minute time out. On test days, saline or opioid agonists were given four hours prior to the test session. During the test session, at the beginning of each time-out period, saline or one of four cumulative NTX doses (0.001 - 30 mg/kg)were given. Pretreatment doses of 3.0 and 10 mg/kg of morphine reduced the ED50 for the ICSS rate-decreasing effect of NTX from > 30 mg/kg to 1.63 and 0.05 mg/kg, respectively. In addition, agonist pretreatment elicited a naltrexone-reversible, dose-related, decrease in the mean frequency at which rats pressed the reset lever (threshold). All p-selective opioid agonists tested, fentanyl > levorphanol > methadone > morphine > and meperidien (listed in order of decreasing potency), produced similar large increases in sensitivity to NTX. The k-selective opioid agonist spiradoline (0.1, 0.3, 1.0 mg/kg) did not induce sensitization. Neither, dextrorphan (3.0 mg/kg), the dextrororatory enantiomer of levorphanol, nor the non-opioid drugs d-amphetamine (3.0 mg/kg) and pentobarbital (18 mg/kg) induced sensitization to NTX. Acute agonist-induced sensitization to NTX in an ICSS paradigm resembles the phenomenon observed with food-reinforced responding. It is produced by mu-opioid agonists stereoselectively, but not by non-opioid drugs. Further, these results are consistent with the theory that acute agonist-induced sensitization to antagonists reflects receptor-mediated changes responsible for physical dependence.

EFFECTS OF HEROIN AND LAAM ALONE AND IN COMBINATION WITH COCAINE ON ACQUISITION AND PERFORMANCE

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We characterized the effects of heroin and LAAM, alone and in combination with cocaine, on the acquisition and performance of conditional discriminations in Old World monkeys. When administered alone, both heroin and LAAM produced dose-related decreases in overall response rate. Neither drug affected accuracy of responding except at high doses that also produced substantial rate-decreasing effects. Cocaine 0.1 mg/kg produced a small shift to the left in the heroin dose-effect curves. At a dose of 0.32 mg/kg cocaine produced a slightly greater shift to the the left in the heroin dose-effect curves (approximately 1/2 log unit). It should be noted, however, that this dose of cocaine decreased response rate and increased errors when administered alone. These results are interesting given the well known abuse potential of this particular drug combination (a "speedball"). The combined effects of LAAM and cocaine tended to be additive, but were less than those obtained with heroin and cocaine. Previously, we have reported that buprenorphine produces large shift to the left in the cocaine dose-effect curve in monkeys responding under this same procedure. Together with the previous study the present data suggest that cocaine interacts with mu opioid agonists in a complex manner. Thus, the liability of the combined abuse of these compounds in terms of their effects on complex behaviors are not as predictable as might be expected.

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CLOCINNAMOX EFFECTS ON INTRAVENOUS SELF-ADMINISTRATION OF MU OPIOID AGONISTS AND COCAINE BY RHESUS MONKEYS: AGONIST EFFICACY AND AFFINITY ESTIMATES

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Intravenous self-administration of the mu opioid agonists alfentanil and nalbuphine as well as cocaine by four male and three female rhesus monkeys was determined according to Winger, *et. al.,* (Drug Alcohol Dep **24**:135-142, 1989) before and 14-20 h after i.v. administration of 0.1 or 1 mg/kg clocinnamox (CCAM). The dependent behavioral measure was responses/s in a FR 30 to 45 s schedule of reinforcement. At 0.1 mg/kg, CCAM shifted the unit dose-response rate curves of alfentanil about 10-fold in all six tested monkeys without depressing the maximum effect (EAm) of alfentanil on rates of responding. At 1 mg/kg CCAM, alfentanil dose-response curves were shifted 500-fold and maximum effects were depressed in two of three monkeys. Responding maintained by nalbuphine was even more profoundly affected by CCAM pretreatment (EAm depression in two of three monkeys at 0.1 mg/kg CCAM, 10-25-fold rightward shift in one monkey; severe EAm depression in all three monkeys at 1 mg/kg CCAM). CCAM also affected responding for cocaine, albeit to a much smaller degree and for shorter periods of time. The behavioral data were analyzed according to Black and Leff (Proc R Soc Lond B **220**:141-162, 1983). The resulting estimates for the agonist efficacy (tau) were 391 for alfentanil and 196 for nalbuphine; the respective K_A values were 0.16 and 0.14 mg/(kg injection). In comparison, a rhesus monkey warm-water tail withdrawal assay (for alfentanil: Zernig, *et. al.,* J Pharmacol Exp Ther 269:57-67, 1994; for nalbuphine, present study) performed at 50¤C yielded efficacy values of 11 for alfentanil and 3.3 for nalbuphine; the respective K_A values were 0.20 and 0.43 mg/kg. Thus, the 57-75-fold higher potency of either agonist in self-administration vs. thermoantinociception was: essentially due to a difference in efficacy.

EFFECTS OF PEMOLINE ON RESPONDING MAINTAINED BY COCAINE AND FOOD IN RHESUS MONKEYS

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The effects of pemoline (1-5.6 mg/kg) on responding maintained under mult FR 30-response schedules of food delivery and intravenous cocaine injections were compared using steady-state performances in four rhesus monkeys. When relatively low doses (10 µg/kg/injection) of cocaine and 1 g banana pellets were used lo maintain responding, rates of responding and numbers of reinforcers taken during a session were generally comparable for both events. Under these conditions, slow i.v. infusions (30ml/15 minutes, beginning 30 minutes before the session) of pemoline selectively decreased cocaine-maintained responding approximately 50%, at doses that had little or no effect on food-seeking behavior. These effects were further compared by 1) giving comparable doses by the oral route of administration, 2) comparing these effects to those of other agents having varying affinities to block dopamine re-uptake, or promote dopamine release. The results are presented in terms of both rate of responding and numbers of each type of reinforcer earned. Emphasis is placed on developing measures which characterize the difference in effect of these agents on both behaviors. The results show that drug-seeking behavior can be selectively attenuated by pemoline in a manner similar to other high-affinity dopamine reuptake inhibitors and dopamine releasers, suggesting that such agents may be useful in treating cocaine abuse.

COCAINE INTRAVENOUS SELF-ADMINISTRATION (IVSA) AND LOCOMOTOR STIMULATION: A COMPARISON OF BALB/C MICE WITH C57BL6xSJL HYBRID MICE

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Profiles of mouse behavior are profoundly dependent on the genetic background of the mice. Strain differences have been demonstrated for complex behaviors, such as learning, and more recently the contribution of genetic differences has been applied to the problems of drug reinforcement and dependence. The behavior of the Balb/c strain, commonly used for immunology studies, was compared with that of a C57xSJL hybrid. The C57 strain is a common parental background strain for generating transgenic and knockout mice. Bath/c mice exhibited increased basal levels of motor activity compared with C57xSJL hybrid mice. The dose-effect function for the locomotor stimulating effects of cocaine was shifted to the left, but blunted, in Balb/c mice. Although both strains learned to discriminate the active from inactive nosepoke hole under a fixed-ratio (FRI) schedule of food reinforcement, Balb/c mice maintained higher rates of responding. Balb/c mice did not acquire cocaine IVSA at a dose of 3.75 or 15 µg/inj (FRI). In contrast, the hybrid mice exhibited > 70% poking in the active hole, as well as stable rates of total drug intake (±20% over three consecutive days) for 15 µg/inj, but not for 3.75 µg/inj. Following training at 15 µg/inj, the hybrid mice exhibited a charactcristic inverted-U shaped dose-effectfunction for cocaine IVSA. Thus, strain differences were revealed in all behaviors examined. Compared to the hybrid mice, the Balb/c mice were more sensitive to the locomotor stimulating actions of cocaine, but they were less likely to acquire IVSA, despite their ability to learn the operant discrimination for food. Mouse strains with a spectrum of sensitivities to drugs of abuse will be useful to investigate the contribution of genetics to the behavioral effects of these drugs and lo reveal physiological differences which may lead to problems of drug reinforcement and dependence.

EFFECTS OF SELF-ADMINISTERED COCAINE ON SCHEDULE-CONTROLLED RESPONDING IN RATS

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The following experiment was designed to investigate the effects of self-administered cocaine on subsequent responding under a fixed-consecutive-number 8 (FCN 8) schedule of food reinforcement, with (signalled) and without (unsignalled) an external discriminative stimulus. Four adult male Wistar rats were implanted with chronic indwelling jugular catheters and were trained to respond under an FCN 8 schedule of food reinforcement. The rats were allowed to intravenously self-administer cocaine (0 to 2.0 mg/kg, iv) during a one or two hour self-administration session. The rats were then transferred to the FCN 8 behavioral chambers and the effects of self-administered cocaine on food reinforced responding were determined. Initially, self-administered cocaine decreased responding under both the signalled and unsignalled components of the FCN 8 schedule. Following repeated exposure, however, tolerance rapidly developed to the effects of cocaine on responding under the signalled component of the schedule, although tolerance did not develop under the unsignalled component even after many months of exposure to the drug.

ACKNOWLEDGEMENTS:

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OPIATE CRAVING DURING NALOXONE-PRECIPITATED WITHDRAWAL IN METHADONE-MAINTAINED VOLUNTEERS

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Use of the term “drug craving” is pervasive but there is limited agreement on its theoretical or practical importance in drug dependence. Craving is defined to be a measurable, subjective state associated with drug-related stimuli, which may co-occur with drug-taking behavior under certain pharmacological and/or ecological conditions. This study assessed whether naloxone-precipitated withdrawal would occasion opiate craving and, if so, whether reported craving would be greater when an opiate could be taken during withdrawal.

Nine methadone-maintained volunteers participated in a repeated measures, randomized crossover design involving four test sessions. Under double-blind conditions, each volunteer was injected intramuscularly with saline on two test days and with 0.2 mg naloxone on lwo test days. On two days (one naloxone and one saline), volunteers were told that if the withdrawal distress was too intense they could choose to receive methadone 30 minutes after the test injection. However, this choice resulted in losing $10. Observer-rated, physiological and subjective measures of opiate withdrawal, mood, and craving were assessed before naloxone or saline injection and for two hours afterwards.

As predicted, naloxone precipitated significant opiate withdrawal. Opiate craving, as measured by a new multi-item scale, showed significant and parallel increases during precipitated withdrawal; in contrast, standard single-item questions failed to show any effect. Contrary to expectation, measures of opiate withdrawal, mood, and craving were not significantly influenced by drug availability, although mean scores tended to be highest in the naloxone/drug availability test session. The present findings have several important implications for conceptualizing and measuring opiate craving, and for investigating the functional relationship between drug craving and drug-taking behavior.

OPIOID AGONIST-ANTAGONIST DRUG DISCRIMINATION IN HUMANS FOLLOWING BUTORPHANOL-SALINE TRAINING

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Human drug discrimination studies permit examination of the relationship between drug discrimination behavior and reported subjective drug effects. Non-physically-dependent opioid abuser volunteers (N=8) were trained to discriminate between i.m. injections of saline and 6 mg butorphanol in daily sessions in a residential laboratory. Following discrimination training they were tested under double-blind procedures with the following i.m. conditions in mixed order: butorphanol (0.375, 0.75, 1.5, 3,6 mg), hydromorphone (0.125, 0.25, 0.5, 1, 2, 3, 4 mg), pentazocine (4, 8, 16, 32, 45, 64 mg), nalbuphine (1.5, 3, 6, 12, 24 mg), and buprenorphine (0.055, 0.11, 0.22, 0.45, and 0.9 mg). Also, the two training conditions were randomly interspersed in order to maintain the quality of the discrimination. All five drugs were discriminated as butorphanol-like -- producing at least 75% butorphanol-like responding al one or more doses. There were only modest between-drug differences in the reported subjective effects. Prior drug discrimination studies have reported greater differences between these same drugs -- both on behavioral discrimination measures and on subjective-effect measures. The contrast with the present results suggests that the specific discrimination trained (*e.g.,* 2-choice versus 3-choice) may influence both discrimination results and the profiles of reported subjective effects.

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EFFECTS OF BUPRENORPHINE AND NALOXONE COMBINATIONS IN OPIATE-DEPENDENT VOLUNTEERS

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Buprenorphine and naloxone combinations may decrease parenteral abuse liability and allow more flexible dose dispensing in opiate abuse treatment programs. The ideal ratio of buprenorphine to naloxone in a sublingual dose formulation will have predominately opiate antagonist effects when administered intravenously and minimal opiate antagonist effects when given sublingually. The physiologic and subjective effects of three dose ratios of buprenorphine to naloxone were compared. Twelve opiate-dependent heroin users were hospitalized for 21 days, stabilized on four daily 15 mg intramuscular doses of morphine, and then challenged under double-blind conditions (on study days 6, 8, 10, 13, 15 and 17) with a series of three intravenous doses of buprenorphine and naloxone (2 mg buprenorphine with either 1 mg, 0.5 mg or 0.25 mg naloxone; 2:1, 4:1, 8:1 dose ratios) or buprenorphine alone (2 mg), morphine (15 mg) or placebo. Daily sublingual doses of buprenorphine (8, 4, 2, 1, 0 mg) were given to assist opiate withdrawal on days 18 to 21. All buprenorphine/naloxone combinations increased opiate antagonist and decreased opiate agonist effects when compared with buprenorphine or morphine. A dose response function on opiate antagonist measures was seen with the 2:1 ratio producing the most intense and sustained withdrawal. The 4:1 and 8:1 ratios had similar antagonist potencies. The 4:1 ratio is being considered as the treatment formulation. This ratio increased global withdrawal, sickness, bad drug and withdrawal scale ratings. The amount subjects were willing to pay for a dose, if illicitly available, was highest for morphine (mean ± SD, $12 ± 10), followed by buprenorphine ($8 ± 10). Subjects were willing to pay a small amount for the buprenorphine/ naloxone 4:1 and 8:1 combinations ($4 ± 7 and $4 ± 5). No subject was willing to pay for the 2:1 buprenorphine/naloxone combination.

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ELECTROPHYSIOLOGICAL AND BEHAVIORAL MEASURES AFTER COCAINE CUE EXPOSURE

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Desensitization to drug-related cues has been actively explored as a potential method to treat cocaine-dependent individuals. However, the functional nature of an individual's response to such cue exposure is presently unknown. The purpose of the present study was to monitor a number of physiologic and behavioral variables in order to more carefully document the profile of this response in cocaine freebase users, occasional users and non users. Nine healthy male subjects provided informed consent and were prepared for electrophysiological recording during the presentation of an "oddball" auditory P3 event-related potential (ERP) task. Electrocardiographic activity and skin temperature were measured at one minute intervals throughout the study. VAS, ARCI and craving questionnaires were delivered via computer. Subjects received the above battery before and after viewing three live minute videotapes. The films were presented in the following order at 30 minute intervals: a neutral cue film on coral reef fish, a stimulated cue film clip from a horror movie and a cocaine cue film of two men buying and smoking crack cocaine. The cocaine cue film had no effect on the non users, but precipitated the following in both cocaine user groups: a marked reduction in skin temperature, a slight increase in LSD scores, no change in craving, no change in heart rate, and a marked reduction in P3 ERP amplitude over occipital sites and an increased amplitude over frontal sites. The horror film increased skin temperature and P3 amplitudes over all sites in all three groups. The profile of ERP changes mimics similar changes that we observed previously in subjects during cocaine-seeking behavior. These data suggest that alterations in brain electrical activity co-vary with the subtle electrophysiological and physiological changes that occur during exposure to cocaine cues and that the effects of cue exposure are similar to those of cocaine-seeking behavior.

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EVALUATION OF THE EFFECTS OF CARBAMAZEPINE ON CRACK-COCAINE CUE REACTIVITY USING A CONTROLLED EXPERIMENTAL DESIGN

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A growing literature supports the reliability and validity of the cue reactivity paradigm as applied to addictive behaviors. The current study used a double-blind placebo-controlled design in an attempt to: (a) establish a standardized neutral cue condition against which to compare cocaine-related cue reactivity; and (b) test the efficacy of carbamazepine (CBZ) in attenuating reactivity to cocaine cues. After extensive screening and one week of treatment, 30 cocaine dependent participants who were enrolled in an inpatient substance abuse treatment program, were scheduled for an initial cue reactivity session. Psychophysiological and self-report responses were collected during baseline, exposure to neutral and cocaine-related cues, and recovery. Participants were then randomly assigned to a CBZ or placebo condition. Pharmacologic treatment was then initiated; and after one week, a second cue reactivity session was conducted. Data were analyzed using ANOVAs/ANCOVAs. Analyses of Session 1 data indicate reactivity during cocaine-related cue exposure differed significantly relative to neutral cue exposure (*e.g.,* SBP, ratings of urge, memories of past crack use, feeling high, feeling like one can taste crack). Analyses of Session 2 data further validated cocaine vs. neutral cue effects, but provided little evidence of effects for CBZ. Overall, these data support the validity of our neutral stimulus procedure, but offer little to suggest the utility of CBZ for attenuating reactivity.

PERSISTENCE OF QUANTITATIVE EEG ABNORMALITY IN CRACK COCAINE WITHDRAWAL

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Pilot work performed in this laboratory indicated a distinctive qEEG profile in withdrawing crack cocaine addicts (Apler, *et. al.,* 1990). In the present study we sought to confirm and extend these findings on a group of 52 subjects undergoing residential drug free treatment for DSM-III-R crack cocaine dependence. Subjects were tested at five to ten days after entry into treatment and again at 30 days (n=39) and six months (n=17). Previous qEEG findings of increased relative alpha power and diminished absolute and relative theta and delta power were replicated. The degree of electrophysiologic abnormality was greater in anterior than posterior leads. The qEEG showed little change in the interval between the first, second, and third observations. The persistence of this qEEG pattern at six months of drug abstinence may indicate on underlying neurophysiologic factor predisposing individuals to addiction, or persistent alterations in neurotransmission as a consequence of chronic cocaine exposure.

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LABORATORY MODEL OF COCAINE-SEEKING BEHAVIOR

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This study was designed to establish a laboratory model of cocaine-seeking behavior that may be useful in screening treatment medications prior to clinical trials. Five males and one female who reported using crack at least two times a week for six months participated in an inpatient study. Subjects underwent a total of four experimental sessions, held on separate days, during which they were exposed to either neutral or cocaine-related stimuli and rated their desire for cocaine. Subjects were exposed to each stimulus condition twice in randomized order. The neutral stimuli consisted of viewing a live minute nature video and making tea, followed by the use of a cocaine smoking device with no dose of cocaine. Cocaine-related stimuli were a five minute video of scenes showing cocaine use and handling cocaine paraphernalia, followed by a 0.4 mg/kg dose of cocaine. After exposure to the stimuli, subjects worked on concurrently-available fixed-ratio tasks either for tokens that could be exchanged for money ($2) or for deliveries of cocaine (0.4 mg/kg). Any combination of a total of seven tokens could be earned each day and tokens earned for cocaine deliveries were administered at a later evening session. The results show subjects reporting significantly greater cocaine craving, as well as a trend for working for cocaine rather than money, after exposure to cocaine-related vs neutral stimuli.

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EFFECTS OF AN ALTERNATIVE REINFORCER AND ETHANOL ON HUMAN COCAINE SELF-ADMINISTRATION

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In this study we examined the influence of an alternative monetary reinforcer and ethanol pretreatment on the probability of cocaine use in humans under controlled laboratory conditions. The experiment included two phases. First, subjects chose between cocaine hydrochloride vs. placebo. Cocaine and placebo were administered intranasally in 10 mg unit doses under double-blind conditions. Second, subjects pretreated with varying doses of ethanol (0-1.0 g/kg) chose between cocaine vs. varying amounts of money (0-$4.00 per choice). Eleven subjects completed the first phase. Those subjects chose cocaine significantly more than placebo, demonstrating dial the drug functioned as a reinforcer. Seven subjects completed the second phase. In those subjects, choice of cocaine decreased as the amount of money in the monetary option increased, demonstrating that the behavioral control exerted by cocaine was dependent on the magnitude of the alternative reinforcer available. Additionally, pretreatment with ethanol increased choice of cocaine over money, with that effect being most discernible in the high-money condition. These results further demonstrate that the availability of an alternative, nondrug reinforcer can decrease the behavioral control exerted by cocaine. They also illustrate how alcohol use can increase the probability of cocaine use, which is consistent with clinical observations regarding the disruptive influence of alcohol use on cocaine abstinence.

DISCRIMINATIVE STIMULUS EFFECTS OF CAFFEINE, EPHEDRINE, AND PHENYLPROPANOLAMINE

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Following the 1970 Controlled Substances Act, the supply of legally available amphetamines was reduced by 80%. This void was filled by "look-alike" drugs which mimic amphetamine's effects. The primary psychoactive substance is usually caffeine or caffeine with one or more sympathomimetic amines such as ephedrine and phenylpropanolaminc. Few data exist on the behavioral pharmacology of these over-the-counter stimulants, but they suggest abuse potential. In this study, seven male stimulant users discriminated between d-amphetamine (30 mg), caffeine (400 mg), and placebo, identified to them by letter code only (a, b, or c). All drugs were administered orally. Following discrimination training, They were exposed to each drug until reaching a criterion of 5/6 correct discriminations in the acquisition testing phase. The discrimination was learned in an average of nine sessions (Range= 5-16). Generalization testing determined dose-response functions for binary combinations of caffeine and ephedrine (0, 100:20, 200:40, 400:80 mg) and caffeine and phenylpropanolamine (0, 50:25, 100:50, 200: 100 mg) and a ternary combination of caffeine, ephedrine, and phenylpropanolamine (0, 50:10:25, 100:20:50, and 200:40:100 mg). All drug combinations produced dose dependent decreases in placebo-appropriate responding and partial generalization to caffeine and d-amphetamine. Presentation of subjective effects data focused on the ternary combination. The ternary combination produced dose related increases on the drug liking visual analog scale, on the A (sensitive to stimulant effects) and MBG scales (sensitive to euphoriant effects which may indicate abuse potential) of the ARCI, and on stimulated and energetic items of the Adjective Checklist. In conclusion, caffeine in combination with ephedrine and/or phenylpropanolamine shares discriminative stimulus effects in common with caffeine and d-amphetamine, a CNS stimulant with known abuse potential. Subjective effects of the ternary combination provide additional support for abuse potential. The three-choice procedure presented here may allow more fine-grained discrimination of drug effects than traditional two-choice procedures.

INHIBITION OF HYDROCODONE (HC) METABOLISM TO HYDROMORPHONE (HM) DOES NOT DECREASE ABUSE LIABILITY

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HC is converted by the genetically polymorphic CYP2D6 to the metabolite HM which is thought to be responsible for its opiate effects. Plasma HM Cmax (mean ± SD) is significantly ($p < 0.001$) lower in poor metabolizers (PMs) than extensive metabolizers (EMs) after HC 10 mg p.o. (0.96 ± 0.29 vs. 5.22 ± 1.77 ng/ml, respectively), while HC plasma levels are not different (Otton, *et. al.,* Clin Pharmacol Ther 1993; 54: 463-472). Quinidine (100 mg p.o. 12 h prior to HC) inhibited CYP2D6 activity in EMs (urinary HC/HM ratios increased 3-9 fold). In a double-blind study 17 EMs and 8 PMs, who could reliably report opiate effects after a HM test dose on a screening day (10 or 20 µg/kg s.c.), were tested with oral HC. Subjects were studied six times and received in a balanced randomized order on separate days placebo or NC 10, 15 or 22.5 mg followed by a repeat of their favourite dose or their favourite dose eight hours after 100 mg quinidine. There were-no signifigant differences on any measures (*e.g.,* pupil diameter; Cole ARCI subscales, POMS, observer ratings; reports of liking) between the EMs and PMs nor between the EMs before and after quinidine. These results suggest that HM accounts for less of HC effects or that the peripheral changes in kinetics do not adequately reflect the central kinetics of HC and its metabolites.

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PERINATAL BUPRENORPHINE EXPOSURE AFFECTS BEHAVIORAL AND CHOLINERGIC DEVELOPMENT IN THE RAT

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The present study was performed to determine whether perinatal exposure to buprenorphine delays the development of striatal cholinergic neurons, as occurs with the full µ-opioid agonist methadone. On day seven of pregnancy, female Sprague-Dawley rats were anesthetized with methoxyflurane and implanted s.c. with 28-day osmotic minipumps filled with buprenorphine (1.5 mg/kg/day) or sterile water. Maternal weight, food and water intake were monitored throughout pregnancy. A significant effect of buprenorphine on maternal food intake was observed ($F[1,14]= 28.481$, $p < 0.0001$), and there were trends toward reductions in maternal weight gain and water consumption. Within 24 hours of birth, litters were culled to 10 and fostered to dams implanted with minipumps containing buprenorphine or water, so that water/water, water/buprenorphine, buprenorphine/water, and buprenorphine/buprenorphine prenatal/postnatal exposure groups were obtained. Maternal osmotic minipumps were replaced with fresh minipumps on postnatal day ten. Littermates were weighed daily out to postnatal day 21. Striatal choline acetyltransferase (ChAT) mRNA was measured by Northern blot analysis in the striata of 10- or 22-day-old rats, using an α-32P dCTP-labelled 300 bp ChAT cDNA probe. Rats exposed to buprenorphine prenatally had a significantly lower birth weight; furthermore, perinatal buprenorphine exposure significantly reduced weight gain out to postnatal day 21 ($F[3,16] = 6.29$, $p < 0.005$). The righting reflex appeared at an earlier age ($F[3,18] = 3.247$, $p < 0.05$) in all buprenorphine-exposed treatment groups. The ratio of ChAT mRNA to 28S RNA was decreased on postnatal day ten, but not on postnatal day 22, in rats exposed to buprenorphine perinatally. Therefore, buprenorphine appears to reduce expression of mRNA for ChAT, which may reflect a delay in the development of striatal cholinergic neurons.

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OPIATES DIRECTLY AFFECT NEURONAL MORPHOGENESIS AND DEATH IN THE DEVELOPING MOUSE CNS *IN VITRO*

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The effects of morphine on Purkinje cell survival and dendritic differentiation were examined in paired, symmetrical (right versus left) organotypic cultures isolated from the cerebella of one and seven day-old ICR mice. Anti-calbindin-D28k antibodies were used to immunocytochemically identify Purkinje cells in whole-mount explants. One explant from each pair was continuously exposed to morphine, morphine plus equimolar concentrations of naloxone, or naloxone alone for seven to ten days in vitro, while the other explant served as a control. In explants derived from one day-old mice, morphine treatment significantly reduced Purkinje cell numbers (EC50 = 3.6 μM) and total dendritic length (EC50 = 49 nM); these effects were prevented by treatment with naloxone. Electron microscopy showed increased numbers of degenerating Purkinje cells in morphine-treated cultures. However, in explants derived from seven day-old mice, morphine treatment had no effect on the number or dendritic length of Purkinje cells. Collectively, these novel results show that opiates per se, through a direct action on the cerebellum, can inhibit Purkinje cell morphogenesis and survivalóperhaps through separate mechanisms. The findings suggest there are critical periods of opiate vulnerability during development, and have implications regarding opiate drug use during pregnancy and early childhood.

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OPIATE MODULATION OF ADENYLATE CYCLASE IN NEONATAL RATS

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Inhibition of adenylate cyclase (AC) mediates many effects of opiate drugs, and up-regulation of AC may contribute to opiate dependence. The purpose of the present study was to investigate the impact of acute and chronic opiate exposure on cAMP production during ontogeny. Studies were performed to determine the ability of DAMGO to inhibit forskolin-, CRF- and PGE_1-stimulated cAMP accumulation in membranes from the locus coeruleus (LC) of 10 day old rats. Stimulation ranged from a seven-fold increase by forskolin, to a 32% increase by CRF. DAMGO (10 μM) inhibited CRF-stimulated cAMP accumulation by 15%, but inhibited forskolin- and PGE_1-stimulated cAMP accumulation, less effectively, 8% and 4% respectively. The α_2-agonist clonidine inhibited cAMP accumulation by 12-17%, irrespective of the stimulating agent. Chronic morphine treatment in neonates up-regulated basal and forskolin-stimulated cAMP levels by more than 30% in the LC, but failed to elevate striatal cAMP levels. Chronic morphine treatment did not alter the ability of DAMGO or clonidine to inhibit cAMP accumulation. The findings of the present study demonstrate that μ-receptors in the LC of neonatal rats are functionally coupled to adenylate cyclase, but the degree of opiate inhibition is stimulator-dependent. In conclusion, the ability of chronic morphine treatment to alter signal transduction pathways in neonatal rats does not appear to be limited. Additionally, the significant up-regulation of AC in developing rats may contribute to opiate withdrawal in neonates.

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INABILITY OF NALOXONE TO ANTAGONIZE FETAL RESPIRATORY DEPRESSION CAUSED BY DYNORPHIN A (1-13) AND U50,488H

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There continues to be interest in the possibility that opioids with selectivity for the κ-opioid receptors might be useful in the clinical management of pain, especially under conditions where morphine-like opioids are contraindicated. The clinical use of opiates as obstetrical analgesics is often associated with neonatal respiratory depression. κ agonists may be ideal for perinatal use since they have been shown not to depress respiratory function at analgesic doses. The effect of κ agonists on fetal breathing is not known. Both the dynorphin peptide (dyn) and κ binding sites have been identified in the brain during early development. In this study, we investigated the effects of dyn A (1-13) on fetal breathing and the possible involvement of the κ-opioid receptor. Intravenous administration of dyn A (1-13) (500 pg/kg) to fetal lambs resulted in a significant time-dependent decrease in hourly breath number. Administration of a selective κ agonist (U50,488H, 1 mg/kg) to fetal lambs also resulted in a significant time-dependent decrease in hourly breath number. Pretreatment with high doses of naloxone (6-12 mg/h) did not block the effects of either dyn A (1-13) or U50,488H. These data indicate that both dyn A (1-13) and U50,488H may act via nonopioid components to depress fetal breathing. More importantly, these results suggest that κ agonists may potentially result in nconatal respiratory depression which is not sensitive to naloxoine antagonism.

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METHADONE MAINTENANCE IN THE TREATMENT OF OPIATE DEPENDENT PREGNANT WOMEN

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Opiate dependence in pregnancy presents an especially difficult problem for health care providers. Minimal data on the safety of methadone maintenance during pregnancy as well as dangers to the fetus from opiate withdrawal make the problem particularly complex. Recent changes in the clinical protocols for pregnant women who are opiate dependent permitted us to evaluate the benefits of methadone maintenance for this high risk population. Outcomes in women admitted prior to the protocol change were compared to those in women admitted after the protocol change. Specifically, the study compared outcomes in opiate dependent women who received a three day methadone taper followed by abstinence-based treatment (n=22) to a group of similar women who were placed on methadone maintenance (n=16). The two groups of women did not differ demographically or in the nature and severity of their drug dependence. The groups did not differ in the number of years of regular opiate use, recent quantity and frequency of opiate use or recent cocaine use. When treatment retention at 40 days post admission was used as a measure of outcome, significant group differences were observed with 69 percent of methadone maintained women retained versus ten percent of abstinence-based women ($p<.0002$). As non compliance with treatment is associated with relapse to substance use and poor maternal and infant outcomes, these data support the value of methadone maintenance as a therapeutic adjunct in the care of pregnant women who are opiate dependent.

COPING, SOCIAL SUPPORT AND SUBSTANCE USE IN CHILDREN OF OPIATE ADDICTS

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Children of substance abusers are at increased risk to develop substance abuse and other behavioral problems. Coping behavior and perceived social support were examined in a cross-sectional study of 97 school-aged children of heroin addicts in methadone treatment. It was hypothesized that positive coping strategies and high levels of adult social support would be significantly related to lower levels of substance use, while negative coping styles would be related to more substance use in this sample. Coping behavior, social support, stress, and substance use, assessed by self-report, were analyzed with multiple regression and logistic regression. Anger/aggression coping and overall avoidant coping strategies (vs. active/approach strategies) were associated with a higher risk for substance use, in particular marijuana. Perceived social support from non-parental adults was found to have a protective effect for children under high levels of stress. These findings suggest that psychosocial interventions for this population should focus on reducing maladaptive coping and enhancing social support from non-parental adults.

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PREDICTORS OF TREATMENT PARTICIPATION AND RETENTION IN AN INTENSIVE OUTPATIENT PROGRAM FOR PREGNANT DRUG ABUSING WOMEN

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Pregnant drug abusing women present for drug abuse treatment with a myriad of problems. Standard treatment settings often fail to address these issues resulting in premature treatment dropout with adverse consequences to mother and infant. To address the needs of this population, an interdisciplinary program with residential and intensive daytreatment services was established at an urban hospital in Baltimore, MD. Despite intensive intervention that includes provision of transportation to and from the program, on-site childcare, etc., 51 percent of women terminated treatment within the first 30 days. The purpose of the present study was to identify sociodemographic and substance use characteristics that were associated with treatment retention and participation. The subjects were N=222 pregnant primary heroin or cocaine dependent women seeking their first admission to the program from November, 1992 to October, 1993. The women were predominantly African-American (87 percent); unemployed (95 percent) and single (79 percent) with a mean age of 27.7 years and a mean estimated gestational age of 25.4 weeks on admission. The women were divided into three groups based on drug use characteristics: N=56 opiate dependent in methadone maintenance; N=101 opiate dependent not in methadone maintenance; and N=62 non opiate dependent (primary cocaine dependent). Analyses were conducted using treatment retention and treatment participation as criterion measures. Any variables significantly correlated with the dependent measure (*i.e.,* age, race, EGA, substance use characteristics (ASI), psychiatric characteristics (ASI), legal characteristics (ASI), and family/social characteristics (ASI)) were controlled for using Analysis of Covariance. Significant differences among groups indicated that opiate dependent women in methadone maintenance stayed in treatment significantly longer ($\underline{M}$=124.9 days, $\underline{p}$,<.001) than both the opiate dependent women not in methadone maintenance ($\underline{M}$ =44.9 days), and the non-opiate dependent women ($\underline{M}$=69.2 days). These data suggest that methadone maintenance is a potent therapeutic adjunct for opiate-dependent pregnant women. By improving treatment retention and participation, methadone maintenance can be of significant benefit in bringing opiate dependent women into closer contact with other badly needed treatment services.

COST-EFFECTIVENESS OF COMPREHENSIVE CARE FOR DRUG ABUSING PREGNANT WOMEN

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Drug abusing pregnant women present with a myriad of obstetric problems and are generally noncompliant with prenatal care and standard drug treatment services. The infants of those women also present with a variety of perinatal problems (*e.g.,* prematurity), and often require extended hospitalization in a Neonatal Intensive Care Unit (NICU). The NICU costs associated with the care and treatment of such infants are substantial (average $1,200/day). In an effort to improve patient compliance with care and thereby improve maternal and infant birth outcomes, comprehensive "one slop shopping" programs have been developed. One of these is the Center for Addiction and Pregnancy (CAP) in Baltimore, MD. To evaluate the cost-effectiveness of the CAP treatment model we compared the costs of NICU medical care for infants of CAP patients (N=110) with those of a demographically similar sample of drug abusing pregnant women not enrolled in drug treatment (N=46). NICU hospitalization rates were cut by over 50% for CAP versus non-CAP infants (10% and 26%, respectively). Average length of NICU stay also decreased substantially, with CAP infants requiring only 6.3 days versus 38.9 days for non-CAP infants. The average NICU costs for infants of CAP patients was only $900 versus $12,183 for non-CAP infants. Thus, the average cost savings was $11,283 per infant. When only those infants requiring NICU admission are examined, the per-infant costs were $7,500 per CAP NICU admission versus $46,700 per non-CAP NICU admission or a savings of $39,200 per NICU infant. The average cost for substance abuse treatment (during pregnancy) at the CAP program is $6,639. Thus the average NICU cost savings is $4,644. Taken together, these data support the cost effectiveness of interdisciplinary treatment programs such as CAP.

TREATMENT PARTICIPATION AND MATERNAL/INFANT OUTCOMES IN PREGNANT DRUG ABUSING WOMEN

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Pregnant drug abusing women typically present in treatment with a myriad of problems and do not fare well in standard drug treatment settings. To address their needs, comprehensive programs have been developed, integrating substance abuse treatment with prenatal care, family planning, and pediatric/child care services. The Center for Addiction and Pregnancy (CAP) is an example of this model of care. During the first 18 months of operation, CAP provided care and treatment to 100 women who remained in the program through labor and delivery. The purpose of the present study was to: 1) Characterize the substance use characteristic of pregnant drug abusing women; and 2) Examine the relationship between patient variables and degree of treatment participation and length of time the patient remained active in the program (retention). Subjects were pregnant women with primary and secondary drug use diagnoses of cocaine (77%); opiate (43%); and alcohol (16%) dependence. Program participation was characterized by quantity and frequency of actual participation and total length of stay. Separate analyses were conducted for treatment participation from admission to delivery and from admission to discharge (up to two years post partum). Patient problem areas were assessed using the Addiction Severity Index (ASI). Multiple regression analysis found four ASI subscale scores significantly predicted patient treatment participation to delivery; composite scores for Family/Social Problems and Alcohol Problems, and interviewer severity ratings for Family/Social and Alcohol Problems. The same four variables predicted participation to discharge with the inclusion of the interviewer severity rating for Legal Problems. Findings suggest that increased attention to these areas will enhance treatment outcome. Due to differential findings between retention and attendance it is suggested that these two similar variables actually measure different constructs and can not be used interchangeably.

PARENTING KNOWLEDGE AMONG DRUG ABUSING WOMEN

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The purpose of this study was to assess changes in parenting knowledge and beliefs among drug abusing pregnant and recently postpartum women participating in a multidisciplinary substance abuse treatment program at the Johns Hopkins Bayview Medical Center, in Baltimore. A 29-item, self-administered, true-false questionnaire was designed to assess parenting knowledge and beliefs in four domains: newborn care, feeding, child development, and drug abuse during pregnancy. Eighty-eight patients (81.1% African American, 65% opiate and 28% cocaine abusers, mean [SD] age 28.5 [4.8], years of education 11.1 [1.7] were pre-tested. The mean percent of correct answers was 53.9%. Less than 40% of women answered correctly questions about managing baby's cry, newborn's signs of over stimulation, time out as a method of discipline, and toilet training. Twenty percent of the women aflirmed that children exposed to drugs during pregnancy will grow up to be "addicts", and more than 60% of these patients considered that children exposed to drugs during pregnancy are born "addicts". Of these 88 patients, 21 were administered the test after receiving two mouths of substance abuse treatment. The results showed a statistically significant increase for the questionnaire total score, and for each test domain. There were no pre- versus post test changes in the question about their belief that children exposed to drugs during pregnancy will grow up to be "addicts", and there was an increase in the percent of women who had the misbelief that infants exposed to drugs during pregnancy are born "addicts". The results of this study suggest that drug abusing women lack of knowledge and have misconceptions about basic parenting skills, and that there are improvements during substance abuse treatment, which may positively affect the outcome of the mother and child.

EVALUATION OF THE DISCRIMINATIVE STIMULUS AND REINFORCING EFFECTS OF NPC 17742 IN RHESUS MONKEYS

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The phencyclidine (PCP)-like abuse potential of 2R,4R,5S-(2-amino-4,5,-(1,2-cyclohexyl)-7-phosphonoheptanoic acid (NW 177421, a potent and selective competitive NMDA receptor antagonist, was evaluated in three different paradigms using rhesus monkeys. Phenobarbital (PHB), a CNS depressant with a similar slow onset and duration of action, was examined for comparison. The discriminative stimulus properties of NPC 17742 were tested in four subjects trained to discriminate PCP from saline under a standard two-lever drug discrimination paradigm. NPC 17742 fully substituted for PCP in three of four monkeys without altering response rates. PHB failed to substitute for PCP in any subject. IV self-administration of NPC 17742 and PHB was tested under an FR schedule of reinforcement in four subjects trained to lever-press for infusions of PCP. In two of the subjects, at least one dose of NPC 17742 was self-administered at levels above those of saline whereas PHB self-administration levels were similar to those for saline. The third study examined IV self-administration of NPC 17742 and PHB under an FI schedule in monkeys trained to self-administer PCP during three daily 20-minute sessions. Response rates for NPC 17742 and PHB were similar to those for saline and were lower than those for PCP. The data show that NPC 17742 has more PCP-like effects than PHB and functions as a weak reinforcer in some subjects. The results show the feasibility of abuse potential evaluation of novel NMDA antagonists and suggests that some differences may exist between PCP and antagonists acting at other sites on the NMDA receptor complex.

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CROSS-SENSITIZATION BETWEEN COCAINE AND BTCP IN THE ABSENCE OF SENSITIZATION TO BTCP

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The phencyclidine analog, BTCP, is a potent DA uptake inhibitor, but binds to a site on the DA reuptake complex different from that of cocaine (Maurice *et. a1.,* 1991). Thus, it is conceivable that its *in vivo* effects, although similar to those of cocaine, may not be identical. To compare further the behavioral effects of BTCP with those of cocaine, male C57BL/6J mice (n=5/group) were injected with BTCP or cocaine (0, 10, 20, or 40 mg/kg, i.p.) for three consecutive days and tested on the fourth day with either BTCP or cocaine (0, 2.5, 10, 20, or 40 mg/kg). During daily sessions, mice were removed from their individual home cages and placed in an observation cage where locomotion was recorded for 30 minutes before and after injection using an automated activity monitor. Repeated injection of cocaine (10, 20, and 40 mg/kg/day x 3 days) shifted the cocaine dose response function to the left, relative to that obtained in chronic saline treated animals; no significant change in the locomotion-increasing effects of BTCP was observed following repeated injection of BTCP. In the cross-sensitization studies, repeated injection of cocaine (20 mg/kg/day) shifted the BTCP dose-response function to the left and upward; repeated injection of BTCP (20 mg/kg/day) shifted the cocaine dose-response function to the left and downward. Thus, cross-sensitization was observed in the presence of sensitization to cocaine, but without sensitization to BTCP. The results suggest that, while BTCP does not produce sensitization under the present conditions, it may partially invoke the same mechanisms which underly sensitization to cocaine.

COMPARISON BETWEEN INHALATION EXPOSURE AND I.V. ADMINISTRATION OF PCP ON MOTOR PERFORMANCE

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One of the most prevalent methods of abusing phencyclidine (PCP) has been by smoking. The purpose of the present study was to compare the pharmacological effects of PCP and its active analog, TCP, on motor performance between intravenous injection and inhalation exposure. Subjects were evaluated in either the rotorod or inverted screen tests 5, 15, 30, 60, and 120 minutes following drug administration. In order to compare the body as well as brain concentrations of PCP between the two routes of administration subjects were either injected or exposed to volatilized [^{3}H]-PCP. The ED50 values of PCP 15 minutes after intravenous administration in the inverted screen and rotorod tests were 1.1 and 1.4 mg/kg, respectively. The empirically determined ED50 value in subjects exposed to volatilized PCP at this time point was 2.8 mg/kg for each test. Although PCP was 2-fold less potent by inhalation route of administration than by intravenous administration, the brain concentrations of PCP equivalents at the ED50 doses were equivalent (0.8 μg/g for each administration route). TCP was more potent than PCP in the inverted screen test, with an ED50 of 0.6 mg/kg. Interestingly, inhalation exposure to volatilized TCP failed to elicit decrements in motor coordination. These findings suggest that TCP may be less likely than PCP to be abused by inhalation. In contrast, inhalation of volatilized PCP resulted in a rapid loss of motor coordination that was of a similar potency as intravenous administration, though of somewhat shorter duration.

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KETAMINE SELF-ADMINISTRATION INCREASES DOPAMINE EXTRACELLULAR LEVELS IN NUCLEUS ACCUMBENS

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PCP-like NMDA receptor antagonists including ketamine (KET) have abuse potential in humans (Cohen, *el. al.,* 1960: Linden, *et. al.,* 1973; Reier, 1971) and several studies have shown that these drugs are self-administered in laboratory animals (Lukas, *et. al.,* 1984). In the present experiments, we used the chronoamperometry technique coupled with stearate-modified graphite-paste electrodes (SGEs) to test the hypothesis that intravenous self-administration of KET would produce an increase in dopamine (DA)extraecllular levels, an effect that is shared by drugs of abuse, in nucleus accumbens (N. Ace.). Rats (n = 13) trained to self-administer KET (1.0 mg/inj) under an FR2 schedule of reinforcement were implanted with SGEs in the N. Acc. bilaterally. Six animals had access to 18 KET injections (1.0 mg/inj) during daily self-administration sessions and seven animals had access to KET (1.0 mg/inj) for 24 hours. DA levels in the N. Acc. were monitored. KET self-administration produced a significant increase in DA oxidation currents in the N. Ace. These findings show that self-administration of the NMDA receptor antagonist KET results in an increase in the DA extracellular levels in N. Acc. This finding is in accordance with the hypothesis that drugs with abuse potential increase DA levels in the mesolimbic system.

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THE ROLE OF GLYCINE AGENTS ON NALOXONE-PRECIPITATED OPIATE WITHDRAWAL IN RAT

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Recent studies suggest that an NMDA receptor systems are involved in opiate withdrawal. While NMDA antagonists lessen withdrawal severity, their PCP-like effects contraindicate clinical use. Because NMDA channels contain sites for the glutamate co-agonist, glycine (GLY), we tested the effects of GLY agents on naloxone (NAL)-precipitated opiate withdrawal in rats. We assessed this using a prcsumed GLY antagonist, felbamate (FEL), and two partial GLY agonists, D-cycloserine (DCS) and HA-966. Groups of rats (n=6 ea) were implanted (s.c.) with three morphine pellets (75 mg ea; NIDA). Three days later, each group received one dose of EEL (0, 100, or 300 mg/kg, i.p.), 60 minutes prior to naloxone (10 mg/kg, s.c.), or one dose of DCS or HA-966 (0, 3, or 10 mg/kg, i.p.) 30 minutes prior to NAL. Withdrawal signs were then rated for 60 minutes by a rater blind to dose group. EEL led to a dose-related decrease in overall severity of naloxone-precipitated withdrawal (Veh: 43.7 ± 2.7; 100 mg/kg FEL: 34.5 ± 3.3; 300 mg/kg FEL: 24.5 ± 1.6; $p<.001$), reduced the occurrences of chews, teeth chatters, and penile grooming (p's<0.05), and produced no PCP-like behaviors (e. g., head weaving). DCS significantly decreased overall withdrawal severity, but not in a dose-related manner. The low dose of HA-966 lead to increases in some withdrawal signs. These results suggest that GLY plays a role in opiate withdrawal and that EEL may be useful for opiate detoxification.

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DISCRIMINATIVE STIMULUS EFFECTS OF LOW AFFINITY NONCOMPETITIVE NMDA ANTAGONISTS

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Low affinity, noncompetitive N-methyl-D-aspartate (NMDA) antagonists are being investigated as therapeutic agents in the treatment of a wide variety of neurological disorders including drug abuse. Recent studies have shown that they may have therapeutic efficacy without producing the serious phencyclidine-like behavioral side-effects (*e.g.,* ataxia and stereotypies) associated with high affinity antagonists (*e.g.,* phencyclidine and dizocilpine). The present experiment examined the ability of low affinity NMDA antagonists to substitute for the discriminative stimulus effects of dizocilpine (K_i = 3 nM; Wong *et. al.,* 1988). Male, Swiss-Webster mice (n = 6) were trained to discriminate dizocilpine (0.17 mg/kg) from saline in a T-maze. High affinity NMDA antagonists, including (-)MK-801, TCP and (+)SKF 10,047 (K_i = 15, 14 and 317 nM, respectively; Wong *et. al.,* 1988), fully substituted for dizocilpine. The lower affinity antagonists, memantine (K_i = 540 nM; Kornhuber *et. al.,* 1991) and ibogaine (K_i = 1,000 nM; Popik *et. al.,* 1994), also substituted for dizocilpine. whereas ADCI (K_i = 11,300 nM; Monn *et. al.,* 1990) did not. There was a positive correlation ($r = 0.97$, $p < 0.01$) between the ED50 for dizocilpine substitution and affinity for the NMDA receptor ion channel, substantiating the conclusion that this behavioral effect is mediated through this site. These results suggest that some low affinity ligands may achieve effective NMDA receptor blockade without producing phencyclidine-like subjective effects.

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Available upon request.

DEPENDENCE ON 1-[1-(2-THIENYL)CYCLOHEXYL]PIPERIDINE (TCP), A PHENCYCLIDINE (PCP) ANALOG, IN RATS

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Previous studies of the primary behavioral dependence producing potential of PCP and dizocilpine (MK-801) demonstrated dose-related disruptions in rat operant behavior when chronic administration (10 days) of these drugs was stopped. The present study investigated the dependence producing liability of TCP in male Sprague-Dawley rats. TCP, a PCP-analog, shares many pharmacological actions with PCP. Using s.c. osmotic minipumps, TCP (1.0-5.6 mg/kg/day) or vehicle was infused to rats trained to respond under a fixed-ratio 30 schedule for food reinforcement. The rats earned all of their daily food rations during four 0.5 hour sessions which occurred every six hours. None of the doses of TCP or vehicle affected response rates during infusions. When the osmotic pumps were removed after 10 days to stop chronic dosing, the two highest dose-groups exhibited a marked suppression of response rates (to about 40% and 15% of pre-drug rates for the 3.2 and 5.6 mg/kg/day groups, respectively). These effects were larger than the effects seen during the infusions and dissipated by about the fifth day after cessation of dosing. The response rate suppression seen at the two higher infusion doses of TCP were similar in magnitude and duration to that seen after cessation of chronic PCP at 10.0 or 17.8 mg/kg/day, or after cessation of chronic MK-801 at 0.32 and 0.56 mg/kg/day, for ten days under comparable conditions. These results demonstrate that TCP produces behavioral dependence, as evidenced by the emergence of a behavioral abstinence syndrome after cessation of dosing.

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NOVEL DEXTROMETHORPHAN ANALOGS THAT ARE POTENT ANTICONVULSANTS SELECTIVELY BIND TO σ_1 SITES

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A series of 17-substituted-3-hydroxy- or 3-alkoxy-analogs of dextromethorphan (DM, (+)-3-methoxy-17-methylmorphinan) was prepared. These compounds were evaluated for their binding affinities at σ_1, σ_2 and PCP sites in rat brain. Further, six of these new analogs were evaluated in the rat maximal electroshock (MES) model for anticonvulsant action and were compared to previously evaluated DM analogs and the parent drug. From this series of compounds, structure-activity relationships were demonstrated at σ_1 sites that, in general, corresponded with previously described models of the σ binding site. The most potent and σ_1-selective compound was 3-ethoxy-17-benzylmorphinan (K_i=8 nM) that was >130 fold selective over the (σ_2 sites and, remarkably, >5000-fold less potent at the PCP sites. None of the compounds were potent at σ_2 sites (K_i range of ~0.5->10 μM) or at PCP sites (K_i range of ~ 0.5-98 μM). Three of these new compounds demonstrated potent anticonvulsant activity and were σ_1-selective. (+)-3-Methoxy-17-(3-methyl-2-butenyl)morphinan produced anticonvulsant actions that were equipotent to DM (ED_{50}=29 mg/kg) while demonstrating >1000-fold selectivity for σ_1 over PCP binding. These data suggest that the σ_1 binding sites may be playing a role in the anticonvulsant actions of these compounds. However, all of these compounds demonstrated low affinity binding at PCP sites and therefore a mechanism involving the NMDA receptor complex cannot be ruled out. Since none of these compounds bind with high affinity to PCP sites, and previously reported analogs of DM were devoid of a PCP-like behavioral profile, they may have potential therapeutic utility in the treatment of seizure disorders. It is anticipated that further evaluation of these compounds in additional seizure models as well as electrophysiological studies may enable the elucidation of the mechanism by which these compounds produce their anticonvulsant effects.

a-ET: A TRYPTAMINE VERSION OF MDA?

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a-Ethyltryptamine or a-ET was briefly used about 30 years ago as an antidepressant but was quickly withdrawn from the market; more recently, it has appeared on the street as a new designer drug: "ET". Although a-ET produces in humans what have been termed LSD-like effects, it is clear that it is not a simple hallucinogen. We demonstrated that a-ET results in stimulus generalization in rats trained to discriminate the hallucinogen DOM from vehicle (Biochem. Pharmacol. 1983, 32, 1267). It is known to produce amphetamine-like stimulant effects. a-ET is also the first tryptamine derivative shown to produce MDMA-like stimulus effects (Pharmacol. Biochem. Behav. 1993, 46, 459). In short, a-ET seems to behave like MDA which is known to produce hallucinogenic, stimulant, and MDMA-like effects. (-)MDA and (+)-MDA are responsible for MDA's hallucinogenic and stimulant actions, respectively. Accordingly, we resolved racemic a-ET and examine its two stereoisomers. MDMA stimulus generalization occurred to (+)-and (-)a-ET (ED50 = 2.0 and 1.3 mg/kg). DOM stimulus generalization occurred to the (+)- (ED50 = 2.7 mg/kg) but not to the (-)-isomer, whereas a (+)amphetamine-stimulus generalization only to (-)a-ET (ED50 = 7.8 mg/kg). Thus, like MDA, this agent is capable of producing different isomer-related behavioral effects. To further investigate this agent, we have now trained rats to discriminate a-ET from vehicle.

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NORIBOGAINE: A MAJOR METABOLITE OF IBOGAINE THAT TARGETS SEROTONIN TRANSPORTERS AND ELEVATES SEROTONIN

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Ibogaine, is a naturally occurring indole alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga*. The use of ibogaine for the treatment of drug dependence has been based on anecdotal reports from addict self-help groups that it may decrease the signs of opiate withdrawal and reduce drug craving for cocaine and heroin for extended time periods. While ibogaine has diverse CNS effects, the pharmacological targets underlying the physiological and psychological actions of ibogaine arc not completely understood. The purported efficacy of ibogaine following single dose administrations has led to the suggestion that a long-acting metabolite of ibogaine may explain in part how the drug reduces craving for psychostimulants and opiates. Recent studies from our laboratory demonstrate that ibogaine is O-demethylated to 12-hydroxyibogamine noribogaine) in laboratory animals and in humans. In radioligand binding screens for activities at specific neurotransporters and receptors, noribogaine demonstrated nanomolar affinity for cocaine recognition sites on the 5-HT transporter. Noribogaine was 50-fold more potent at the 5-HT transporter than at the DA transporter. Ibogaine and 12-hydroxyibogamine were shown to be equipotent at the dopamine transporter. *In vivo* microdialysis was used to evaluate the acute actions of ibogaine and noribogaine on the levels of DA and 5-HT. Administration of noribogaine produced a marked dose-related elevation of extracellular 5-HT. Ibogaine and noribogaine failed to elevate DA levels in the nucleus accumbens over the dose range tested. The elevation in synaptic levels of 5-HT by noribogaine may heighten mood and attenuate withdrawal dysphoria. The effects of the active metabolite on 5-HT transmission may account in part for the potential of ibogaine to interrupt drug-seeking behavior in humans.

ALTERED SENSITIZATION TO COCAINE FOLLOWING PRENATAL COCAINE EXPOSURE

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Adult rats gestationally exposed to cocaine were assessed for their behavioral response to acute and chronic ip cocaine. Subjects were born to dams of one of three prenatal treatment groups: C40-daily injections of 40 mg/kg/3cc cocaine HCl sc from gestational days 8-20; PF-daily injections of saline along with pairfeeding and watering to C40 females: and LC-uninjected controls. Adult (60-75 days of age) offspring from each prenatal group were placed into one of two groups: chronic ip 20 mg/kg cocaine or chronic ip saline. Injections were given once daily in a lest chamber for four consecutive days (chronic phase). Animals were placed into the chamber five minutes pro-injection and remained there for 30 minutes post-injection. Forty-eight hours after the fourth injection, all animals received a challenge dose of 10 mg/kg cocaine ip (test day). Behavior of the animals during the subsequent 30 minutes was recorded. Test day results showed that, unlike controls, animals in the chronic cocaine group who were prenatally exposed to cocaine failed to develop behavioral sensitization as measured by stereotypy. While not differing from controls in acute response to cocaine during the chronic phase, C40 animals chronically treated with saline exhibited high levels of stereotypy in response to their first experience with cocaine on lest day, perhaps as a result of cross-sensitization with daily saline injection stress.

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EFFECT OF MATERNAL HISTORY OF COCAINE ON PUPS' BEHAVIORAL VULNERABILITY TO COCAINE

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Pups born of female, Long-Evans rats exposed to cocaine or cocaine vehicle during pregnancy (Group COC and Group VEH), exposed to cocaine prior to and during pregnancy (Group Long-term cocaine, LTC) or pair fed to Group LTC (Group PF) were fostered to nonexposed control subjects and then assessed at Gestation Day 50 for their self administration of cocaine via a schedule-induced polydipsia preparation (see Lau *et. al.,* 1992). Specifically, in daily sessions pups received delivery of food pellets once a minute for 60 minutes during which time they had unlimited access to various concentrations of cocaine (0 - 0.32 mg/ml) in a glucose/saccharin solution. Prenatal cocaine exposure (with and without a maternal history of cocaine) increased overall consumption of cocaine over that of the pair-fed and vehicle controls for female subjects. A maternal history of cocaine in combination with prenatal cocaine exposure increased overall consumption of cocaine in male subjects above that of the pair-fed and vehicle controls and that of the prenatal cocaine exposure only group. Consistent with other reports on behavioral vulnerability to cocaine, this study demonstrates that prenatal (and/or maternal cocaine history) influences the subsequent responsivity to cocaine, in this case its self-administration. Since overall consumption by males with a combination of maternal and prenatal cocaine exposure was greater than that by males with prenatal cocaine exposure only, the possibility exists that prior published reports of failures to find prenatal cocaine effects on other behavioral measures may have resulted from the failure to expose mothers to cocaine prior to pregnancy.

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PREGNANT COCAINE DEPENDENT WOMEN: FACTORS RELATED TO RETENTION IN TREATMENT

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This study is part of a NIDA Perinatal-20 Research Demonstration Grant that investigated the effectiveness of comprehensive residential (MSP) and outpatient (OP) treatment for pregnant cocaine dependent women. Sixty-four subjects were enrolled in treatment (32 MSP; 32 OP). At intake there were no differences in personal characteristics of age, income, race, parity, cocaine use and treatment history. Depression, locus of control, and social support were similar, but treatment groups differed significantly in daily stressors (MSP > OP, $p < .05$) and psychiatric symptoms reported during lifetime (MSP > OP, $p < .05$). Overall, the quantitative results showed few differences between groups in perinatal outcomes, psychosocial assessments at three months postpartum or retention in treatment. Although twice as many OP clients departed by two months postpartum, no differences were found in mean months in treatment overall (MSP, 6.3; OP, 5.8). Partial correlations indicated that treatment retention was associated with daily stressors, satisfaction with emotional state and life coping, locus of control, parenting self-esteem, compliance with prenatal care and abstinence during pregnancy. The findings identified differential durations and goals in treatment among cocaine dependent women and suggest that treatment programs must be flexible in offering the services women need and at the points they are required in order to promote retention in treatment.

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BIRTH OUTCOME IN COCAINE-ABUSING WOMEN FOLLOWING THREE MONTHS OF DRUG TREATMENT

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Seventy-two polydrug (cocaine plus other drugs) using pregnant women participating in a drug treatment program were followed prenatally (starting on average about three months from birth) to 18 months post-partum. This report follows the women from intake to birth, a period of approximately three months. As part of their treatment the women participated in random urine toxicology tests. Women in the drug treatment program, who decreased their drug use at least 50% from intake, gave birth to infants who had, longer gestational periods, weighed more at birth, and had larger head circumferences. These women were not found to be different from those who continued to use drugs more heavily with respect to demographic variables such as education, marital status, age at intake, or admitted drug use at intake on the Addiction Severity Index, although women who used drugs less often showed fewer self-reported symptoms of anxiety on the MCMI-2 and a tendency to show fewer symptoms for borderline pathology.

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COMPARISON OF PUBLISHED MECONIUM ASSAYS

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Scientific papers which compare testing of neonatal or maternal urine with testing of meconium for the determination of drug exposure during pregnancy are numerous. Some of these articles conclude that there is, in fact, no difference between urine and meconium as a true indicator of drug exposure. While urinalysis is fairly standardized throughout testing laboratories, the same cannot be said for the extraction of drugs from meconium. We analyzed meconium specimens by three different published procedures. The results were widely inconsistent, with one procedure correctly diagnosing only 19% of true positives. We conclude that the comparison of urinalysis with meconium testing cannot be scientifically proven unless a reliable meconium extraction and analysis procedure is employed. Further, our research has shown the existence of a cocaine metabolite in 95% of meconium samples which is not present in urine. The compound is the only metabolite present in 23% of meconium specimens. We conclude that a direct comparison of urine and meconium results based unreliable meconium extractions is scientifically incorrect.

ASSESSMENT OF PERCEPTUAL ORGANIZATION IN COCAINE-EXPOSED INFANTS

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Previous studies indicated that neonates prenatally exposed to cocaine demonstrate poor attention modulation compared with normal neonates. Rather than modulate, they prefer higher amounts of stimulation. We hypothesize that these early attentional effects translate to perceptual differences at older ages, but require assessment using tasks appropriately shifled lo higher processes. We use the visual recognition memory (VRM) paradigm that attempts to evaluate such processes using two tasks. Infants are grouped according to intrauterine cocaine exposure as assessed by meconium toxicology, urine toxicology and/or maternal report. Neither Rose's nor Fagan's procedures yielded differences across groups. Novelty scores on Rose's task were low in all groups (53%). Although on the Fagan we obtained appropriate preferences for the novel stimulus (57%), again no group differences emerged. We then extracted the average length of look during Fagan's procedure across familiarization and test trials combined, as the utility of this manner of analyzing fixation data with atypical populations such as infants exposed to alcohol has been presented by In the present data, the cocaine-exposed had shorter durations of looks across age, and may represent a behavioral style in cocaine-exposed infants that could underlie information processing and obtaining information about the environment. Results will be discussed in terms of exploring methodologies to tap into emerging perceptual/cognitive abilities and to more accurately differentiate among risk infants.

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PARENTING BEHAVIOR AND MOTHER-CHILD INTERACTION NOT RELATED TO MATERNAL COCAINE USE

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To study the behavioral effects of prenatal cocaine use, we interviewed mothers and videotaped mother-child pairs in various play situations. It has been asserted that cocaine use (COC) is associated with less optimal parenting behavior and parent-child interaction than in non-cocaine using dyads (NON). Both COC (N=18) and NON (N=19) infants were selected from a general pediatric clinic and affiliated drug treatment program. Groups had similar parity, maternal education and child gender. Cocaine users were older and more likely to be African American than Hispanic in ethnicity. Infant age was similar in both groups (range 5-33 months). Blinded coders scored videotapes using measures of child focused attention, Parent/Caregiver Involvement Scale (PCIS), Parenting Stress Index, and Teaching Scale. No significant differences between groups were found in any indicators of interaction or parenting behavior. COC mothers had more instructive and discipline behaviors on the PCIS, but the quality and appropriateness of these did not differ from NON mothers. These results do not support greater interactional difliculties between COC infants and their caregivers. Failure to detect differences may be due to small sample size. selection factors. confounding, insensitive measures, or no real differences between groups.

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MATERNAL ATTENTIVENESS OF COCAINE ABUSERS DURING CHILD-BASED ASSESSMENTS

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Few studies of cocaine-exposed children have focused on parenting behaviors which may exacerbate or compensate the effects of prenatal drug exposure. Studies in other high risk groups suggest that maternal attentiveness is related to child play, language development, exploratory behavior, and the quality of the mother-infant interaction. Cocaine abusing and non-cocaine-using women were recruited from a hospital-based prenatal clinic or at delivery and assessed at 3 months (n=64), 6 months (n=80), 12 months (n=90), and 18 months (n=53) post-delivery. Videorapes taken during developmental assessments of the children were rated on an incidental measure of maternal attentiveness. At the three month follow-up time point only, cocaine-abusing mothers spent a lower percentage of time being attentive (97.5%) than did non-cocaine-using mothers (99.1%). Cocaine abusers also had more changes in their level of attentiveness (8.84) than did controls (4.71) and had shorter durations of maximum attentiveness (411 seconds) than did control mothers (698 seconds). However, these differences did not remain significant at 6, 12, or 18 months. In addition, there were no between group differences on separate behavioral ratings of maternal activity, affect, distraction, engagement, or intrusiveness. The findings did not provide strong support for the hypothesis that cocaine abusing mothers would be less attentive than non-cocaine-users to their children.

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INTERVENTION OUTCOMES AFTER TWO YEAR FOLLOW-UP OF COCAINE-USING POST-PARTUM MOTHERS

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A sample of 163 women similar as to drug of choice (89% cocaine), unemployment (96%), never married (85%) race (African American 93%) with age 28 ± 3.9 years, education 11-12 years, 2.9 ± 1.4 live children, and 2.1 prior pregnancies were referred by hospital workers and randomly assigned: residential before outpatient, outpatient only, or no active treatment. Research case managers collected data at four month intervals out to two years. Despite child care and transportation treatment compliance was poor, fewer than 25% could be considered "compliant", even when loosely defined. The random Tx-variable showed residential to be marginally more effective than the other groups in reducing average cocaine use over the two year period. Cocaine use was estimated from multiple indicators including normalized serial hair, urine, and self-report. Post-basal data were represented by a vector of log change scores of the average of multiple repeated measures in order to provide more stable estimates of change in several domains including: cocaine, seven ASI subscales, global psych severity, depression, self-esteem, difficult life. Two general categories of predictors were studied: resource utilization (a combination of those utilizing treatment and/or case management), and baseline characteristics of the mothers. The outcome vector was tested against predictors (MANOVA). Resource utilizers were more likely to show positive changes; the change estimates for the entire vector was significant. Among all variables tested against the change vector, none were as strongly predictive of positive change as having taken any prenatal care during pregnancy (F+3.7, P=.000). Also, better basal scores on the two NCAST procedures, the feeding and teaching scales, higher education and social support were predictive of positive change over two years. Two year survival of 57% in research favored women > 24 years age. Findings suggests women who had the most going for them at baseline, and who took the best advantage of resources, gained the most. Inversely, it suggests that even within a high risk sample, the women with the greatest need, fewest resources, and likely the highest risk are the least changeable.

BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XIX. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE, INC. (1995)

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THE DRUG EVALUATION COMMITTEE (DEC)

The analgesic testing program of DEC originated with the appointment of Dr. Nathan Eddy to direct the pharmacology program in the University of Michigan in 1930, a year after the CPDD was formed as the Committee on Drug Addiction of the National Research Council, NAS (Eddy, 1973; May and Jacobson, 1989). A CPDD Preclinical Testing Program was established in 1983 lo initiate the evaluation of stimulants and depressants and incorporate the on-going analgesic testing program. The Program eventually became known as the CPDD's Animal Testing Committee and in 1989 the name changed lo the CPDD Drug Evaluation Committee (DEC). This CPDD committee is responsible for gathering in vivo and in vitro information on potentially abusable drugs.

The DEC currently examines, and/or does methodological research on drugs with analgesic, stimulant, depressant, and/or hallucinogenic actions, and provides information relating to the physical dependence potential and abuse liability of these drugs to pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, as well as to the World Health Organization. The DEC data have been used by NIDA, the DEA, and the FDA for the determination of the scheduling of these drugs, and have been recently used by researchers in their search for medications to treat drug abuse. DEC is one of the few organizations able to provide such information using predetermined, established, published methodology in a completely independent and unbiased manner. The data which arc obtained by DEC, under the auspices of the CPDD, are published within three years and can be seen in this Monograph, and preceding Monograph issues (Aceto *et al.,* 1995b; Jacobson, 1995; Winger *et al.,* 1995; Woods *et al.,* 1995), as well as in various journals (Aceto *et al.,* 1989; May *et al.,* 1994).

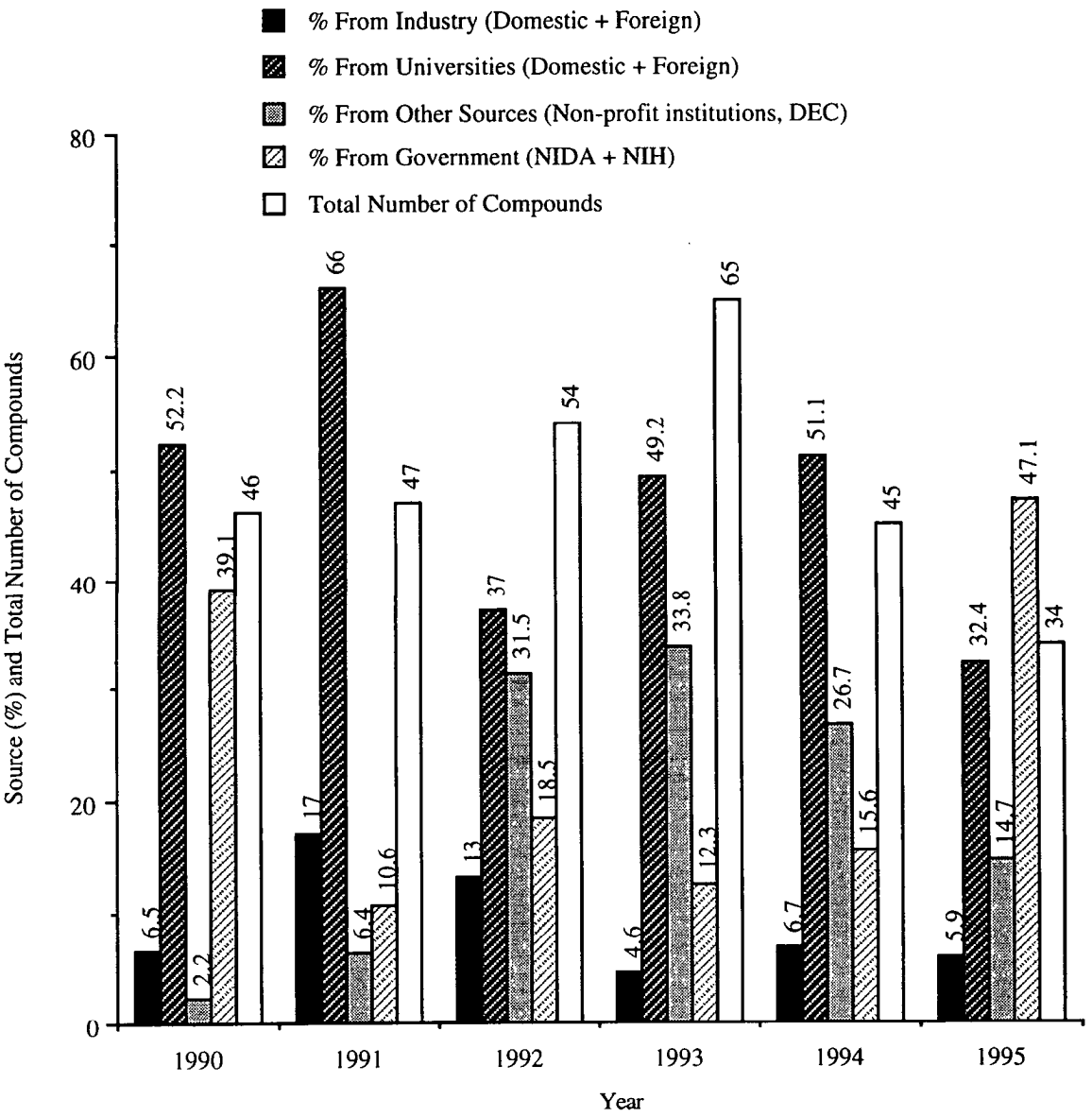
MEMBERS OF THE DRUG EVALUATION COMMITTEE (DEC)

The analgesic testing groups are based in the Medical College of Virginia (MCV; Drs. Harris, Aceto, Bowman, and May) and at the University of Michigan (UM, Drs. Woods, Mecdzihradsky, Smith. and Winger). The stimulant/ depressant testing groups were al MCV (Drs. Patrick and Harris), UM (Dr. Winger), and the University of Mississippi (Dr. Woolverton). In August. Louisiana State University (Dr. France) will initiate its testing program. Dr. T. Cicero (Washington University) is the chairman of the DEC.

STATISTICS

The sources, and total number of compounds, released for publication during the past six years (1990 - 1995) can he seen in Fig. 1. Except for 1991-1992, the percentage of drugs received from pharmaceutical industry has remained about the same (ca. 6% during this time period). A much larger percentage of our drugs come from chemists in universities, domestic and foreign, and this percentage can he seen to he variable (*e.g.,* 66% of the released compounds originated in universities in 1991, contrasted with 32% this year). The number of compounds which come from non-profit institutions (14.7%) have appreciably lessened since 1992-1993. This year almost half of our compounds came from various government groups (NIDA and NIH). The two compounds released for publication after testing by the stimulant/depressant testing groups came from the WHO, and NIDA. The WHO-submitted drug, zipeprol, is the subject of a recent paper submitted to Drug and Alcohol Dependence by the involved DEC scientists (Aceto *et al.,* 1995a).

FIG. 1. DEC ANALGESIC PROGRAM: SOURCES AND NUMBER OF COMPOUNDS TESTED (1990-1995)



EXPERIMENTAL OBSERVATIONS

Table 1 lists the names and assigned NIH numbers of the compounds examined this year, and notes the Tables in which they are shown. Tables 2 - 8 present the structures and a summary of the biological activities of compounds evaluated as analgesics, as obtained from Aceto *et al.* (1996), and Woods *et al.* (1996), and Table 9 summarizes the work of the stimulant/depressant groups. The compounds in Tables 2 - 8 are grouped according to their molecular structure (*e.g.,* 4,5-epoxymorphinans, morphinans, fentanyl-like compounds, etc.) in order to facilitate the comparison of their molecular structure and biological activity. As seen in Tables 2 - 4, the 4,5-epoxymorphinan class of compounds are still being explored, and are the source of new, interesting, and potent agonists (*e.g.,* NIH 10801, Table 2) and antagonists (*e.g.,* NIH 10805, Table 2). The 4,5-epoxymorphinans, exemplified by morphine, codeine, and heroin, were initially described over a century ago - yet the properties of compounds in this class still fascinates both chemists and pharmacologists. Another 4,5-epoxymorphinan, the

zwitterion NIH 10775 (Table 2) displays reasonably potent antinociceptive activity, yet does not substitute for morphine in the SDS assay in monkeys; it is possible that it is metabolized differently in the various animal species used for these assays, exemplifying the importance of using several assays in different animal species. This compound has little affinity for opioid receptors in the binding assay (as expected for phenolic esters) and in the vas deferens preparation. NIH 10842 (Table 2, oxymorphindole) appears to be a selective δ agonist-antagonist in the vas deferens preparation, and is potent and selective in the binding assays. Subtype-selective opioids are valuable and are the subject of considerable contemporary research. The endoethano and endoetheno derivatives of the 4,5-epoxymorphinans have been explored for some time (buprenorphine is one of the useful relatives in this class); new members of this class are shown in Table 3. NIH 10811 (Table 3) is an especially potent antagonist. The compounds listed in Table 4 come from a series of 4,5-epoxymorphinans explored at LMC, NIDDK, to find a suitable SPECT imaging ligand. The ^{123}I labelled NIH 10826 has been noted to be a highly selective p-agonist and is being explored for SPECT imaging purposes.

Data on α--levomethadol (NIH 10837, Table 5), a probable metabolite of LAAM, were needed for toxicity studies. Although NIH 10837 was first synthesized in 1950 by Dr. E. L. May at NIH (as NIH 4552) it was not tested at UM at that time. It is interesting to note that although it is reasonably potent in antinociceptive assays and in a binding assay (where it shows selectivity for the μ-opioid receptor), it does not display the typical opioid-like property of suppressing abstinence in the SDS assay in monkeys.

Except for NIH 10789, the fentanyl-like compounds in Table 6 are atypically impotent as antinociceptives. Most interesting for theoretical chemists, only one of the two compounds (NIH 10788 and 10789) which differ at one chiral center, appears to behave as an opioid. This is very common in the structurally rigid classes of opioids where stereochemistry is known to be important for opioid activity (*e.g.,* in the 4,5-epoxymorphinan class, (-)- but not (+)-morphine has opioid activity).

Among the miscellaneous compounds, those with structures uncharacteristic of the known classes of opioids, NIH 10815 (Table 7). has been noted to be a selective, potent, δ--receptor agonist by others (Calderon *et al.,* 1994). In our hands it displayed only weak antinociceptive activity. The vas deferens preparation gave data in general accord with the previously published work. Zipeprol (NIH 10843, CPDD 0042; Table 8) was examined by both the analgesic and stimulant/depressant groups. Although it showed weak antinociceptive activity in one (PPQ) assay, it completely suppressed abstinence in morphine-dependent monkeys in the SDS assay.

ABBREVIATIONS USED IN TABLES 2 - 8

Rounded numbers are used in the tables; precise values and details of the procedures are given in the MCV (Aceto *et al.,* 1996) and UM (Aceto *et al.,* 1996) reports.

1) MOUSE ED50/AD50: antinociceptive assays (sc injection); confidence limits are listed in the MCV report (Aceto *et al.,* 1996).

HP = hot plate (morphine ED_{50} = 0.8 (0.3-1.8))

PPQ = phenylquinone (morphine ED_{50} =0.23 (0.20-0.25))

TF = tail-flick (morphine ED_{50} = 5.8 (5.7-5.9))

TFA = tail-flick antagonism vs. morphine (naltrexone AD_{50} = 0.007 (0.002-0.02); naloxone AD_{50} = 0.035 (0.01-0.093)).

I = inactive, without a reasonable dose-response relationship, or insufficiently active for statistical analysis.

2) IN VITRO (Data from UM) (Woods *et al.,* 1996)

RBH = binding affinity in rat cerebrum membranes (displacement of 0.5 nM [^{3}H] etorphine) in the presence of 150 mM NaCl (morphine EC_{50} = 23.6).

NE = no effect.

NOTE: Contemporary EC_{50} data cannot be directly compared with those from reports before 1985 (Jacobson, 1996) which were obtained under "-NaCl" (without NaCI) conditions.

BIND = subtype selective binding affinity using monkey brain cortex memhranes (data from UM) (Woods *et al.,* 1996). Selectivity for μ, κ, and δ opioid receptors determined with [^{3}H]-DAGO, [^{3}H]-*p*-Cl-DPDPE and [^{3}H]-U69.593, respectively.

VD = electrically stimulated mouse vas defercns EC_{50} values. Partial agonist indicated by % inhibition of twitch in parenthesis; [A] = antagonism by naltrexone.

SE = slight effect on twitch.

NE = No significant agonist or antagonist effect.

ANT = Antagonist activity. Selective antagonist activity at μ, δ, and/or κ receptors is footnoted.

The antagonist effect may or may not be competitive. Compounds which suppress the twitch and are not antagonized by naltrexone or other narcotic antagonists are said to be non-opioid agonists (*e.g.,* clonidine, a non-opioid agonist, can suppress the twitch but is not antagonized by naltrexone). Compounds which bind with reasonable affinity in the RBH assay and do not suppress the twitch in the VD may have narcotic antagonist properties. The opioid receptor at which the drug exerts its antagonist effect is determined by testing various concentrations of the drug to induce a blockade (antagonism) of the suppression of the twitch in the VD preparation caused by sufentanil (μ), DSLET δ or U50.488 κ (Woods *et al.,* 1996).

3) IN VIVO: in the rhesus monkey (from MCV (Aceto *et al.,* 1996); from MCV or UM prior to 1988).

SDS = single-dose-suppression (Parenthesized numbers = dose range studied, in mg/kg)

NS = no suppression

CS = complete suppression

PS = partial suppression

Other Studies (noted in the footnotes to the tables)

A) In Rat: RI = rat continuous infusion (data from MCV) (Aceto *et al.,* 1996)

1) SM = substitution for morphine

NS = no substitution for morphine

CS = complete substitution

PS = partial substitution

2) PPD = primary physical dependence

B) In Rhesus Monkey:

1) PPt-W = studies in non-withdrawn monkeys (data from MCV) (Aceto *et al.,* 1996)

PW = precipitated-withdrawal at dose levels, in mg/kg, indicated in parentheses &/or comparison with naloxone [N].

SP = slight precipitation

NP = no precipitation

2) ND = studies using non-dependent monkeys (data from MCV) (Aceto *et al.,* 1996)

M-like = morphine-like effect.

3) PPD = primary physical dependence (data from MCV) (Aceto *et al.,* 1996)

4) SA or SI = self-administration or self-injection (data from UM) (Woods *et al.,* 1996)

NE = no effect

High = codeine-like

IN = intermediate between saline and codeine

SE = slight effect

5) DD = drug discrimination (data from UM) (Woods *et al.,* 1996)

NE = no effect

CS = complete substitution

6) MA = monkey analgesia (data from UM) (Woods *et al.,* 1996)

7) RF = respiratory function (data from UM) (Woods *et al.,* 1996)

Previous Reports

Previous work on a compound is noted using the year listed in the monograph title (*e.g.,* work cited as "1992" indicates that the work was included in "Problems of Drug Dependence 1992", which was published in 1993). Note that the monograph's publication date may be one year after the titled year of the monograph. Complete details of the original work on a compound can be found in the Annual Report from either UM or MCV.

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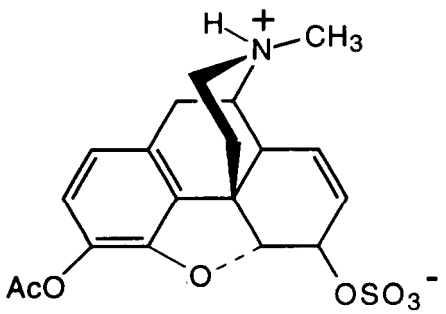
TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

NIH#	NAME	TABLE #-Evaluator[a]
10747	3-(4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino] piperidine)-propanoic acid, methyl ester. HCl	6-MCV/UM
10764	N-(Phenyl)-N-[1-(1,2,3,60tetrahydro-1,3-dimethyl-2,6-dixoxo-7H-purin-7-yl)ethyl)-4-methoxycarbonyl-4-piperidinyl]propanamide oxalate	6-MCV/UM
10767	*R*-(+)-3-Amino-1-hydroxy-2-pyrrolidone	7-MCV/UM
10775	Dihydromorphine 3-acetate 6-sulfate	2-MCV/UM
10788	(±)-8-(2-Hydroxy-2-phenylethyl)-2-ethyl-t-6-methyl-1-phenyl-1, 3, 8-triazaspiro[4.5] dec-2-ene-r-4-one .2HCl	6-MCV/UM
10789	(±)-8-(2-Hydroxy-2-phenylethyl)-2-ethyl-c-6-methyl-1-phenyl-1, 3, 8-triazaspiro[4.5] dec-2-ene-r-4-one .2HCl	6-MCV/UM
10801	18-Chloro-4,5α-epoxy-3-hydroxy-α,α,N-trimethyl-6α, 14α-ethenoisomorpinan-7 α-methanol.HCl	2-MCV/UM
10804	Metathebainone.HCl	5-MCV/UM
10805	1-Chlorodiprenorphine oxalate	2-MCV/UM
10810	N-Cyclopropylmethyl[7 α,8α,2',3']cyclopentano-1'-[S]hydroxy-6,14-endoethenotetrahydronororipavine.HCl	3-MCV/UM
10811	N-Cyclopropylmethyl[7 α,8α,2',3']cyclopentano-1'-[S]hydroxy-6,14-endoethenotetrahydronororipavine.HCl	3-MCV/UM
10812	2-Nitrobuprenorphine.HCl	3-MCV/UM
10813	2-Nitrodiprenorphine.HCl	3-MCV/UM
10814	2-Nitronaltrexone.HCl	3-MCV/UM
10815	(+)-4-[(α*R*)-α-(12S,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide	7-MCV/UM
10816	(±)-2,4-Dimethyl-5-(3-hydroxyphenyl)morphan.HBr	5-MCV/UM
10817	7-Chloro-7-cyano-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2methyl-6,8a-ethanoisoquinoline	7-MCV/UM
10818	Nω-Nitro-L-arginine methyl ester	7-MCV/UM
10819	Nω-Nitro-L-arginine	7-MCV/UM
10823	3,6α,14-Trihydroxy-17-methyl-4,5 α-epoxymorphina	4-MCV/UM
10824	3-Acetoxy-6α,14-dihydroxy-17-methyl-4,5α-epoxmorphinan	4-MCV/UM
10825	3-Acetoxy-6α-trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5-α-epoxymorphinan	4-UM
10826	3-Acetoxy-14-hydroxy-6ß-iodo-17-methyl-4,5 α-epoxymorphinan	4-MCV/UM
10827	3,14-Dihydroxy-6ß-iodo-17-methyl-4,5 α-epoxymorphinan	4-MCV/UM
10828	3,6ß,14-Trihydroxy-17-methyl-4,5 α-epoxymorphinan	4-MCV/UM
10829	3-Acetoxy-6ß,14-dihydroxy-17-methyl-4,5 α-epoxymorphinan	4-MCV/UM
10830	3-Acetoxy-6ß-trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5 α-epoxymorphinan	4-MCV/UM
10831	3-Acetoxy-14-hydroxy-6α-iodo-17-methyl-4,5α-epoxymorphinan	4-MCV/UM
10832	3,14ß-Dihydroxy-6α-iodo-17-methyl-4,5α-epoxymorphinan	4-MCV/UM
10837	α-(-)-6-Dimethylamino-4,4-diphenyl-3-heptanol .HCl (α-l-levomethadol,α-l-methadol)	5-MCV/UM
10842	Oxymorphindole .HCl	2-UM
10843	Zipeprol[4-(2-methoxy-2-phenylethyl)-α-(methoxyphenylmethyl)-1-piperazineethanol .2HCl	8-MCV/UM
10850	(-)-Epibatidine hemioxalate (= natural base)	8-MCV
10851	(-)-Epibatidine hemioxalate (= unnatural base)	8-MCV
CPDD 0042	Zipeprol[4-(2-methoxy-2-phenylethyl)-α-(methoxyphenylmethyl)-1-piperazineethanol .2HCl	9-MCV, UM, UMS
CPDD 0043	4-Bromo-2,5-dimethoxy-ß-phenethylamine .HCl	9-MCV, UM, UMS

TABLE 2. 4,5-EPOXYMORPHINANS[a]



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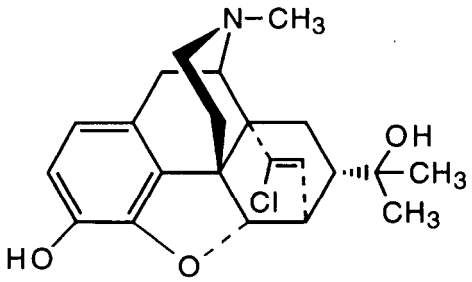

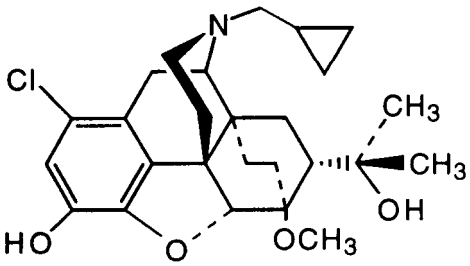

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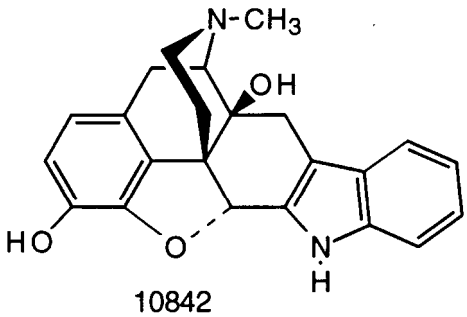


10842

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	H P	PPQ	T F	T F A	RBH (nM)	VD (nM)	S D S
10775	5.0[b]	0.7	4.2	I [b]	2500	2405 (85%)[A][c]	NS (3,16)[d]
10801	0.03	0.01	0.03	I	3.7	26.8 (99%)[A][e]	CS (150xM)
10805	I [f]	I [f]	I[f,g]	0.09[f]	0.61[f]	ANT[f,h]	NS (0.01-0.02)[f,i]
10842	-	-	-	-	BIND[j]	155 (78%)[A][k]	-

a) See text for explanation of column headings and abbreviations.

b) Toxic.

c) Weak, partial μ-opioid agonist.

d) Inconsistent dose-response; attenuation of withdrawal. Lack of effect, compared with mice antinociceptive data, may reflect metabolic differences.

e) Relatively selective μ-agonist.

f) Previously reported - 1993.

g) Apparent pA_2 vs. M: non-competitive antagonist; apparent pA_2 vs. NIH 10672 (κ-agonist): 8.0; time course study - acts promptly, duration of action >4 h.

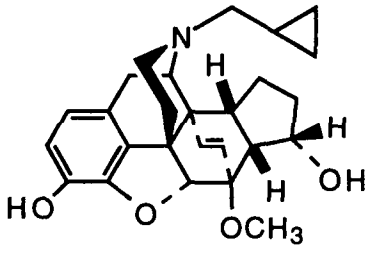
h) Non-selective; insurmountable at κ.

i) Exacerbates withdrawal; PPt-W: PW (like naloxone).

j) BIND: μ: 157 nM; δ: 2.29 nM; κ: 297 nM.

k) Selective δ-antagonist.

TABLE 3 (CONTINUED). 4,5-EPOXYMORPHINANS[a]



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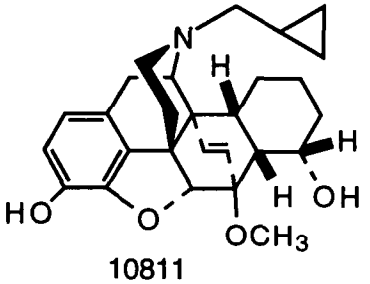

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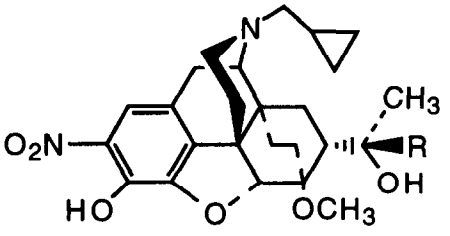
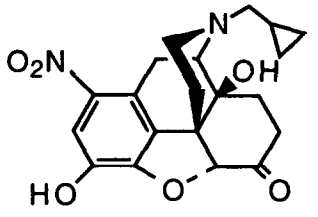


10812 R=*t*-Bu
10813 R=Me



10814

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH#	HP	PPQ	T F	TFA	RBH (nM)	VD (nM)	SDS
10810	I	I	I	0.4	0.91[b]	8.7 (78%)[A][b,c]	NS[d]
10811	I	I	I	0.02	0.59[b]	0.86 (99%)[A][b,c]	NS[e]
10812	I	I	I	I	3.81[b]	6.6 (56%)[NA][b,f]	NS[g]
10813	I	I	I	I	140[b]	410 (44%)[A][b,h]	NS[i]
10814	I	1.2	4.3	3.8	196[b]	3.4 (23%)[A][b,j]	NS[k]

a) See text for explanation of column headings and abbreviations.

b) Previously reported - 1993.

c) Relatively selective p-agonist.

d) Exacerbated withdrawal (~ 0.1xN); longer duration of action than N.

e) Exacerbated withdrawal; PPt-W: PW (5xN).

f) Very weak mixed antagonist, slightly more potent at κ and δ.

g) Did not exacerbate withdrawal.

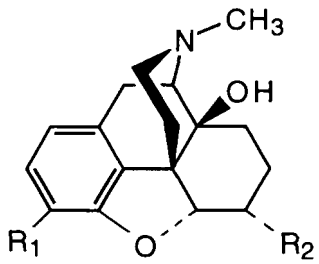
h) Competitive antagonist at μ and δ, insurmountable antagonist at κ.

i) May have exacerbated withdrawal.

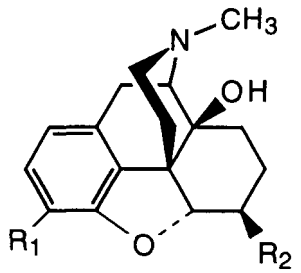
j) Competitive antagonist at μ and δ, insurmountable antagonist at κ.

k) Exacerbated withdrawal; strong convulsant (monkey died).

TABLE 4 (CONTINUED). 4,5-EPOXYMORPHINANS[a]



10823 R_1=OH, R_2=OH
10824 R_1=OAc, R_2=OH
10825 R_1=OAc, R_2=OSO_2CF_3
10831 R_1=OAc, R_2=I
10832 R_1=OH, R_2=I

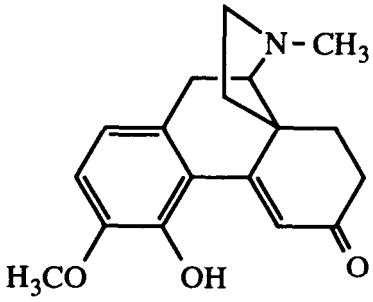


10826 R_1=OAc, R_2=I
10827 R_1=OH, R_2=I
10828 R_1=OH, R_2=OH
10829 R_1=OAc, R_2=OH
10830 R_1=OAc, R2=OSO_2CF_3

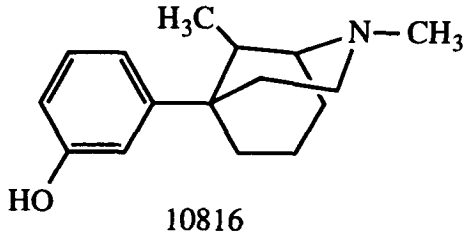
	MOUSE ED_{50}/AD_{50}				IN VITRO		MONKEY
NIH #	HP	PPO	TF	TFA	RBH (nM)	VD (nM)	SDS
10823, 7472	1.2	0.11	0.4	I	94	1000 (97%)[A]	CS (3xM)
10824	0.61	0.14	0.3	I	517	642 (94%)[A][c]	CS (10xM)
10825	-	-	-	-	1590	276 (91%)[A][d]	-
10826	0.03	0.02	0.02	I	259	287 (90%)[A][c]	CS (20xM)[e]
10827	0.08	0.008	0.04	I	31	472 (98%)[A][c]	CS (60xM)
10828	2.73	0.36	1.37	I	304	472 (98%)[A][c]	CS (M-like)
10829	3.83	0.24	2.49	I	478	261 (86%)[A][c]	CS (M-like)
10830	0.22	0.04	0.09	I	634	295 (100%)[A][c]	CS (10xM)
10831	0.06	0.009	0.02	I	242	6500 (100%)[A][f]	CS (75xM)
10832	0.02	0.1	0.02	I	40	92 (100%)[A][g]	CS (300xM)

a) See text for explanation of column headings and abbreviations.
b) Previously published - 1962.
c) Relatively selective μ-agonist.
d) Partial μ-agonist.
e) Typical μ-agonist.
f) Weak μ- and δ-agonist
g) μ- and δ-agonist.

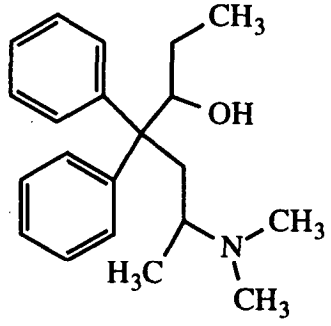
TABLE 5. MORPHINAN, METHADOL, PHENYLMORPHAN[a]



10804



10816



10837 (4552,α-Levomethadol)

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	HP	PPO	TF	TFA	RBH	VD (nM)	SDS
10804	I	I	I	I	>6 μM	104 (30%)[SA][b]	NC[c]
10816	I	15.8	I	I	-	-	NS[d]
10837 (4552)	4.9	1.9	13.9	I	BIND[e]	134 (31%)[NA][f]	NS[g]

a) See text for explanation of column headings and abbreviations.

b) Low potency partial agonist, or non-opioid.

c) Perhaps D_2 blockade - near catalepsy.

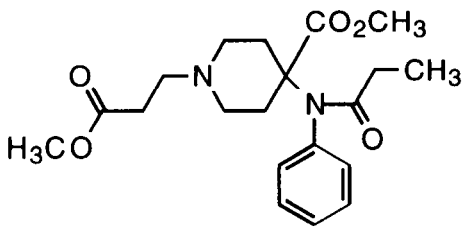
d) Observed tremors, chewing, increased respiratory rate.

e) BIND: μ= 248 nM, δ and κ = >6 μM

f) Weak μ antagonist.

g) Effects not dose-related; delayed, questionable suppression observed.

TABLE 6. FENTANYL-LIKE COMPOUNDS[a]



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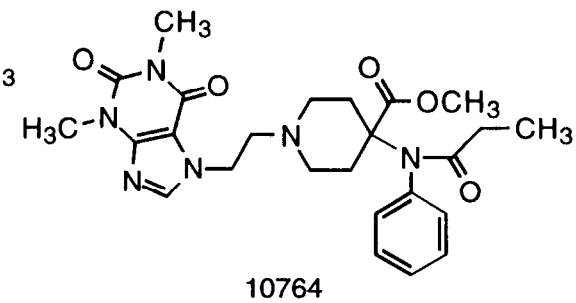
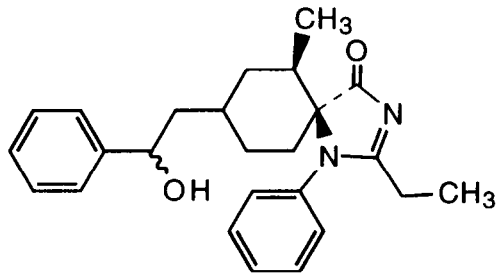
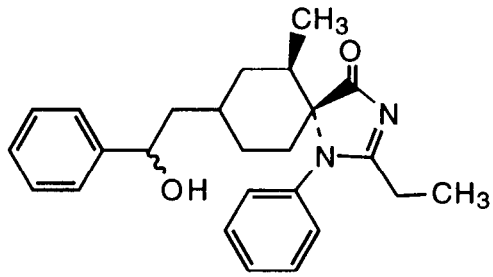


10764



10788



10789

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	HP	PPO	T F	TFA	RBH (nM)	VD (nM)	SDS
10747	I	I	I [b]	I	117	110 (100%)[A][c]	PS (3000xM)[d]
10764	I	I	I	I	>6000	220 (31%)[NA][e]	PS (6.25)
10788	I	I	I	I	2500	3.3 (71%)[NA][f]	NS (3-12)
10789	0.05	0.003	0.011	I	6.25	4.96 (99%)[A][g]	CS (60xM)

a) See text for explanation of column headings and abbreviations.

b) Straub tail at 30 mg/kg; μ-agonist for 10 min, no action after 20 min; increased locomotion blocked by N in all antinociceptive tests.

c) μ-agonist.

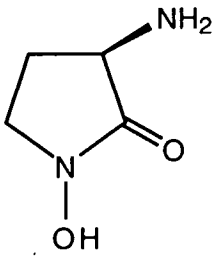
d) Atypical attenuation of withdrawal, but μ-like overall.

e) Low efficacy agonist, no antagonist activity.

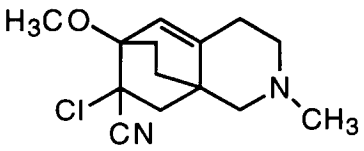
f) No significant agonist or antagonist activity.

g) Potent μ-agonist.

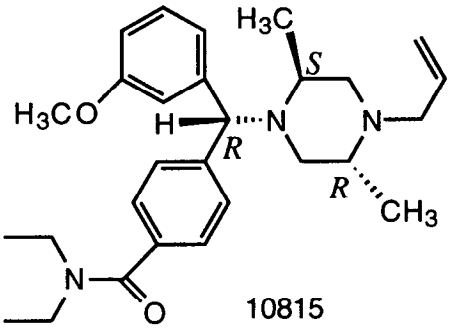
TABLE 7. MISCELLANEOUS[a]



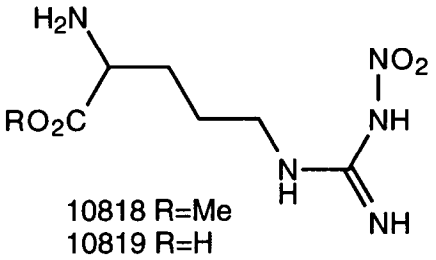
10767



10817



10815



10818 R=Me
10819 R=H

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	HP	PPO	TF	TFA	RBH (nM)	VD (nM)	SDS
10767	I	1.8[b]	I	I	>6000	I[c]	NS (2.5,10)
10815	I	3.8	I	I	>6000	6.4 (100%)[A][d]	NS (3.15)[e]
10817	I	I	I	I	>6000	1.3 (33%)[NA][f]	PS(4); NS(16)[g]
10818	I	I	I	I	>6000	2800 (80%)[A][h]	NS (4,16)[i]
10819	I	I	I	I	>6000	66 (63%)[NA][j]	NS (3,15)[k]

a) See text for explanation of column headings and abbreviations.

b) Naloxone AD_{50}: 14% @ 1 mg/kg.

c) No significant activity as agonist or antagonist.

d) Relatively selective δ-agonist.

e) No exacerbation of withdrawal, ataxia, slowing; perhaps non-opioid.

f) Minimal antagonist activity at highest concentration.

g) Possible stimulant at higher dose.

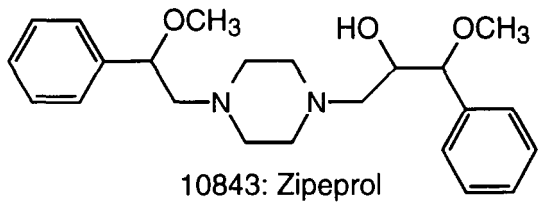
h) Weak, selective μ-agonist.

i) Observed depressed respiration, confusion.

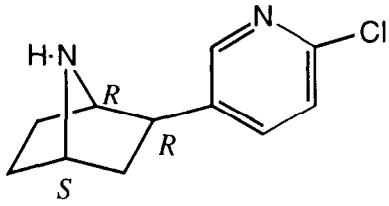
j) Devoid of significant opioid activity.

k) Possible μ-antagonist activity, may exacerbate withdrawal.

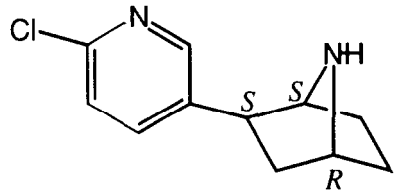
TABLE 8 (CONTINUED). MISCELLANEOUS[a]



10843: Zipeprol



10850: (+)-Epibatidine. hemioxalate (corresponds to natural (-)-base)



10851: (-)-Epibatidine. hemioxalate (corresponds to unnatural (+)-base)

		MOUSE ED50/AD50			IN VITRO	MONKEY	
NIH #	HP	PPO	TF	TFA	RBH	VD (nM)	SDS
10843	I	8.7	I	I	BIND[b]	148 (31)[NA]	CS (0.25xM)[c]
10850	-	1.6[d]	12.5[e]	-	-	-	-
10851		0.8[f]	8.6[g]	-	-	-	-

a) See text for explanation of column headings and abbreviations.

b) BIND: μ = 369 nM, κ = 67 μM, δ = 60 μM.

c) Rapid onset, short duration of action; depressant actions.

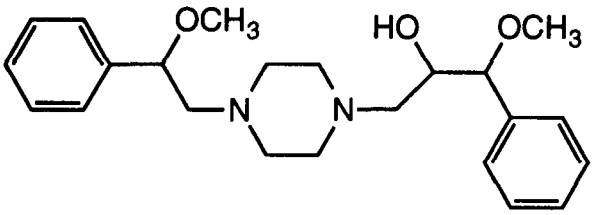
d) Naloxone vs NIH 10850 ED_{50} - inactive; mecamylamine pA_2 = 6.2.

e) Naloxone vs NIH 10850 ED_{80} - no dose-response (51%@10).

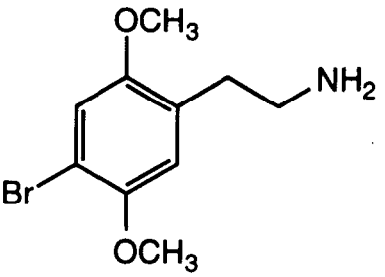
f) Naloxone vs NIH 10851 ED_{50} = 0.02 mg/kg.

g) Naloxone vs NIH 10851 ED_{80} = 0.1 mg/kg.

TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD 0042: Zipeprol



CPDD 0043

CPDD#	SLA[a]	IS[b]	PD-S[c]	SA[e]	DD[f]
0042 (NIH 10843)	Stimulant/ Depressant[g]	Impaired[h]	NS[i]	Reinforced	No[k]
0043	Erratic[l]	Impaired[m]	NS[n]	Possible[o]	No[p]

a) Spontaneous locomotor activity (mouse).
b) Inverted screen assay (mouse).
c) Physical dependence - substitution for pentobarbital (rat infusion).
d) Physical dependence - primary (rat infusion).
e) Self-administration (monkey).
f) Drug discrimination (intragastric administration, monkey).
g) Mild stimulation @ 40 mg/kg, profound depression @ 100, 175 mg/kg followed by mild excitation.
h) @ 40 mg/kg and up. Mild effects on central excitability at nontoxic doses; greatest effect is dose-related depression persisting 60 min, followed by mild stimulation. Not a classical stimulant or depressant,
i) Slight, not significant, reduction of behavioral signs.
j) In methohexital- and alfentanil-trained monkeys (quadazocine reduced reinforcing potency in latter, suggesting opioid effect.
k) No drug-appropriate responding in either amphetamine (AMPH)- or pentobarbital (PB)-trained monkeys. Unlikely to have AMPH- or PB-like effects in humans. Low therapeutic index.
l) Mild depressant @ 6 mg/kg, mild stimulant @ 50 mg/kg, followed by mild depression.
m) Dose-related impairment (5-6 x pentobarbital); not clearly depressant.
n) Appears to promote sedative and muscle-relaxant effects without promoting barbiturate-type dependence.
o) Served as reinforcer in some monkeys at some doses; at larger or smaller doses, only saline-like behavior.
p) Not predicted to have AMPH- or PB-like effects in humans.

EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (1995)

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This report contains information on opioid abuse liability evaluations on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained can involve both *in vitro* evaluation in opioid binding assays and smooth muscle preparations. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys. Each of these assays is described below. Usually when limited information is provided (*e.g., in vitro* assessment only), it is because the sample provided by the submitter was insufficient to carry out further evaluation.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD. The compounds, which come originally from pharmaceutical companies, universities, government laboratories, and international organizations are submitted to Dr. Jacobson.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information and (4) a recommended starting dose. After the evaluation is complete and the report submitted to Dr. Jacobson, the submitter is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter has up to three years before release of the structure is required. When the structure is released all of the data on the compound are reported to the Drug Evaluation Committee.

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil or fentanyl; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio et al. (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in isolation chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a

subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection before the start of the cycle. Each cycle lasts 15min and consists of an initial 10-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than 100 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily sessions are comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. sessions consist of between two and six discrete, 15-min cycles with each cycle. Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled

shocks for 30 seconds by pressing five times consecutively (*i.e.,* fixed-ratio 5) the lever appropriate for the solution administered during the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 ml/kg) or drug (0.01 mg/kg naltrexone) during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one time out and for that cycle and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (*e.g.,* irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (*e.g.,* alfentanil; France and Woods, 1989; France et al., 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone (*i.e.,* precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent (*i.e.,* withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

THERMAL ANALGESIA IN RHESUS MONKEYS

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40°, 50°, or 55° C and the latency until the tail is withdrawn from the thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40° C water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40° C water does not produce tail withdrawal in rhesus monkeys (Dykstra and

Woods, 1986); however, if a monkey fails to keep its tail in 40° C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40°, 50°, and 55° C water. The order in which the three temperatures are presented is varied among subjects. If the latencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40° C water and less than 5 seconds for 55° C water, monkeys receive the test compound. The test is identical to the pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes or less and the order in which temperatures are presented varies among subjects and across cycles. The interinjection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (*e.g.,* alfentanil) or κ (*e.g.,* U-50,488) opioid agonist.

RESPIRATORY STUDIES IN RHESUS MONKEYS

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO_2 in air (France and Woods, 1990; Howell et al., 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% CO_2 in air is delivered at a rate of 10 1/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume (V_T) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO_2. The last 3 minutes of exposure to CO_2 are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the interinjection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (*e.g.,* alfentanil).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produce an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period

occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four components of a session. Other procedural details are given in Winger *et al.* (1989).

DISPLACEMENT OF RADIOLABELED LIGAND BINDING

Details of the binding assay based on the displacement of ^{3}H-etorphine in rat brain membranes have been described previously (Medzihradsky *et al.,* 1984). Briefly, aliquots of a membrane preparation from rat cerebrum are incubated with ^{3}H-etorphine in the presence of 150 mM NaCl, and in the presence of different concentrations of the drug under investigation. Specific, *i.e.,*

TABLE I

EC_{50}'s of representative opioids for displacement of 0.5 nM ^{3}H-etorphine from rat brain membrane, and inhibition of the twitch of the mouse vas deferens preparation.

Compound	BINDING* EC_{50} (nM)	MVD
DPDPE	---	5.52
U50,488	---	6.29
Fentanyl	36.2	37.1
DAMGO	23.9	81.3
Etorphine	0.37	0.0068
(-)Cyclazocine	0.53	11.9
Naltrexone	0.63	__
Bremazocine	1.42	0.29
UM 1071R**	1.55	__
Sufentanil	1.60	4.43
(-)SKF 10047	3.93	__
Ethylketazocine	6.60	11.6
Ketazocine	14.1	1.18
Morphine	23.6	395
DSLET	43.0	1.71
Dextrorphan	<6000	1010

* In the presence of 150 mM NaCl.

** 1R-5R-9R-2"R-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan hydrochloride

opioid-receptor-related interaction of ^{3}H-etorphine is determined as the difference in binding obtained in the absence and presence of an appropriate excess of unlabeled etorphine. The potency of the drugs in displacing the specific binding of ^{3}H-etorphine is determined from log-probit plots of the data. See table I for representative results with different opioids.

To enhance the characterization of novel opioids, we are also investigating their selectivity in binding to μ-, δ-, and κ--opioid receptors in membranes from monkey brain cortex. Thus, we are now providing K_i values of the tested compounds in displacing the following radiolabeled opioid ligands:

etorphine (nonselective, reflects opioid character),
sufentanil or Tyr-D-Ala-Gly-(Me)Phe-Gly-ol (DAMGO); (μ selective),
[D-Pen^2-D-Pen^5]enkephalin (DPDPE; δ selective),
U-69,593 κ (selective).

Using the receptor-specific assays, we have described the selectivity of various established opioids in brain membranes of different species (Clark *et al.,* 1988). The selection of *monkey brain* as the tissue for the selective binding assays strengthens the correlation between this *in vitro* assessment and the behavioral evaluation of the tested compounds. In the **ANNUAL REPORT,** the results of the selective binding assays are listed under "Binding in monkey brain cortex." See table II for representative results with different opioids in rat and monkey brain.

ISOLATED, ELECTRICALLY-STIMULATED MOUSE VAS DEFERENS PREPARATION

The development of new, highly selective antagonists such as the reversiblereceptor antagonist norbinaltorphimine (Smith et al., 1989) and the competitiveδ receptor antagonist ICI-174864 have made possible the evaluation of selectivity of opioid agonists and antagonists by use of the mouse vas deferens preparation. Male, albino ICR mice, weighing between 25 and 30 g, are used. The mice are decapitated, the vasa deferentia removed, and 1.5 cm segments are suspended in organ baths which contain 30 ml of a modified Kreb's physiological buffer. The buffer contains the following (mM): NaCI, 118; KCI, 4.75; $CaCl_2$, 2.54; $MgSO_4$, 1.19; KH_2PO_4, 1.19; glucose, 11; $NaHCO_3$ 25; pargyline HCl, 0.3; and disodium edetate, 0.03. The buffer is saturated with 95% O_2 - 5% CO_2 and kept at 37° C. The segments are attached to strain gauge transducers and suspended between two platinum electrodes. After a 30-min equilibration period, the segments are stimulated once every 10 sec with pairs of pulses of 2 msec duration, 1 msec apart and at supramaximal voltage. See table III for potencies of representative agonists.

TABLE II

Inhibition of radiolabeled sufentanil, DPDPE and U69,593 binding in rat and monkey brain. In membranes from rat cerebrum and monkey brain cortex, the inhibition of specific equilibrium binding of 0.5 nM [^{3}H]sufentanil, 1.5 nM [^{3}H]DPDPE and 1.5 nM [^{3}H]U69,593 by five different concentrations of the listed compounds was investigated in the presence of 150 mM NaCl (modified from Clark et al., 1988).

Compound	EC_{50} (nM) [^{3}H]Sufentanil	[^{3}H]DPDPE	[^{3}H]U69,593
Rat cerebrum			
DAMGO	13.2	690	
Sufentanil	1.25	45.0	
Morphine	31.4	422	
β-FNA	6.99	43.9	
β-CNA	1.29	7.48	
Naloxone	6.37	14.3	
Etorphine	0.60	1.13	
Buprenorphine	1.07	1.12	
Bremazocine	1.79	1.12	
Superfit	576	16.5	
DSLET	121	1.05	
ICI- 174,864	58900	59.0	
DPDPE	7720	6.44	
U50,488	7230	13 100	
U69,593	3 8000	13400	
Monkey cortex			
Sufentanil	1.18	81.1	>10000
DPDPE	18900	4.21	>10000
U69,593	10700	17000	8.41

The following antagonists are studied: naltrexone HCl, ICI- 174864 [N,N-diallyl-Tyr-Aib-Aib-Phe-Leu-OH) and norbinaltorphimine. The antagonists are added to the organ baths 15 minutes before the determination of cumulative concentration-effect relationships for the various agonists. See table III for the potencies of different competitive antagonists studied in relation to prototypic agonists. EC_{50}'s are calculated by probit analysis, and pA_2 values are determined to assess relative potencies of antagonists.

All drugs which are submitted for evaluation are studied in the following manner: 1) the

submitted drug is tested on the vas deferens preparation in the absence and in the presence of a concentration of naltrexone sufficient to block μ,κ and δ receptors. 2) If the submitted drug inhibits the twitch and its actions are blocked by naltrexone, it is evaluated further in the absence and presence of ICI-174864 and norbinaltorphimine used in concentrations at which these antagonists are selective for δ and κ receptors, respectively. 3) If the submitted drug is a partial agonist or devoid of agonistic activity at opioid receptors, it is evaluated further as an antagonist against the following agonists: sufentanil (μ selective), DSLET (δ selective) and U50,488(κ selective). If the submitted drug has antagonistic activity against any or all of the receptor-selective agonists or upon any of the other preparations used in the Drug Evaluation Unit, the type of antagonism (competitive, noncompetitive, irreversible) is determined. For further details of the procedure and for a description of experiments in which β-funaltrexamine was used see Smith (1986). Drugs studied in the preparation prior to 1987 were evaluated with the protocol reported in the 1985 Annual Report.

TABLE III

Potencies of antagonists assessed in the mouse vas deferens

	pA_2 values* determined with three agonists		
	Sufentanil (μ)	U50,488 (κ)	DSLET (δ)
Antagonist			
Naltrexone	8.76	7.74	7.41
Naloxone	7.99	6.90	7.35
Cyprodime	7.41	6.15	5.98
Nalbuphine	7.23	6.31	5.76
Naltrindole	7.71	7.38	9.44
ICI-174,864	<5.00	<5.00	7.90

*The pA_2 value is the negative logarithm of the molar concentration of antagonist necessary to shift the agonist concentration-effect curve to the right by a factor of 2-fold.

SUMMARY OF TESTS PERFORMED

The compounds which were evaluated at the University of Michigan during the past year, and the individual tests which were performed are shown in table IV. Also shown are dates of Reports to the Biological Coordinator, Dr. A.E. Jacobson, in which results are reported.

TABLE IV
SUMMARY OF TESTS PERFORMED

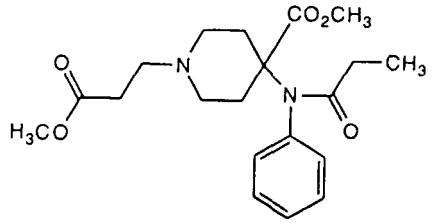
NIH #	S A	MVD	BIND	D D	ANLG	RSP	REPORT*
10747	-	+	+	-	-	-	02/10/92
10764	-	+	+	-	-	-	02/12/92
10767	-	+	+	-	-	-	02/18/93
10775	-	+	+	-	-	-	10/30/92
10788	-	+	+	-	-	-	03/05/93
10789	-	+	+	-	-	-	05/03/93
10801	-	+	+	-	-	-	05/26/93
10804	-	+	+	-	-	-	04/23/94
10817	-	+	+	-	-	-	02/14/94
10818	-	+	+	-	-	-	02/14/94
10819	-	+	+	-	-	-	02/14/94
10823	-	+	+	-	-	-	05/30/94
10824	-	+	+	-	-	-	05/20/94
10825	-	+	+	-	-	-	05/20/94
10826	-	+	+	-	-	-	05/20/94
10827	-	+	+	-	-	-	05/20/94
10828	-	+	+	-	-	-	07/06/94

Table IV (continued)

NIH	SA	MVD	BIND	DD	ANGL	RSP	REPORT*
10829	-	+	+	-	-	-	07/06/94
10830	-	+	+	-	-	-	05/20/94
10831	-	+	+	-	-	-	07/06/94
10832	-	+	+	-	-	-	07/27/94
10837	-	+	MCB	-	-	-	03/24/95
10842	-	+	MCB	-	-	-	02/15/95
10843	+	+	MCB	+	+	-	09/20/94

* Date report was submitted to CPDD Biological Coordinator. MCB = Monkey Cortex Binding

NIH 10747 **3-(4-Methoxycarbonyl-4-[1-oxopropyl)phenylamino] piperidine)-propanoic acid, methyl ester hydrochloride [or: N-phenyl-N-[1(2-methoxycarbonylethyl)-4-methoxycarbonyl-4-piperi-dinyl]propanamide hydrochloride]**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 117 nM in the presence of 117 nM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

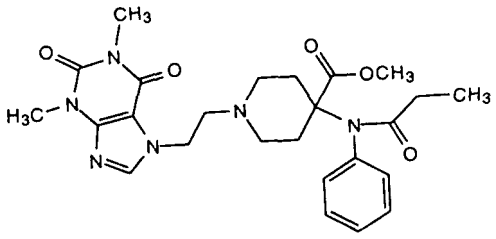
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	106.6 ± 70.9	100		9
Naltrexone (100 nM)	2042.9 ± 1310.6	100	19.2	3
ICI-174864 (100 nM)	48.2 ± 5.7	100	0.5	3
Nor-BNI (10 nM)	57.0 ± 26.4	98.7 ± 1.3	0.5	3

SUMMARY

NIH 10747 was active in both preparations. It was selectively blocked by naltrexone. Thus, NIH 10747 was a μ agonist in the *vas deferens* preparation.

* * *

NIH 10764 **N-phenyl-N-[1-(2-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purin-7-yl)ethyl)-4-methoxycarbonyl-4-piperidinyl]propanamide oxalate**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of >6,000 nM (50.4% inhibition at 6 μM) in the presence of 150 mM NaCl.

NIH 10764 (continued)

MOUSE *VAS DEFERENS* PREPARATION

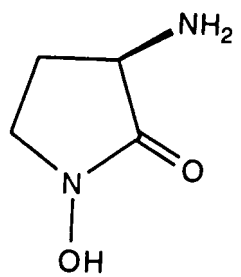
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	219.1 ± 132.3	31.1 ± 6.0		3
Naltrexone (100 nM)	32.8 ± 5.3	19.9 ± 1.1	0.1	3

SUMMARY

NIH 10764 had no significant opioid activity in the binding assay. It acted as a low-efficacy agonist on the isolated, electrically-stimulated mouse *vas deferens* preparation. The inhibitory effects of NIH 10764 were not antagonized by naltrexone, 100 nM. When tested as an antagonist, NIH 10764, 30 μM, did not affect responses of the *vas deferens* to sufentanil, a μ-opioid receptor agonist, to DSLET, a δ opioid receptor agonist, or to U50,488, a κ-opioid receptor antagonist. Thus, NIH 10764 appears to be devoid of significant opioid agonist or antagonist activity.

* * *

NIH 10767 R-(+)-3-Amino-1-hydroxy-pyrrolidone



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of >6,000 nM (2.9% inhibition at 6 μM) in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

NIH 10767 was studied on the isolated, electrically stimulated mouse *vas deferens* preparation in concentrations which ranged from 1 nM to 30 μM. Concentrations up to 30 μM had no appreciable effect on this preparation. When tested as an antagonist at a concentration of 30 μM, NIH 10767 caused slight shifts to the right in the concentration-effect curves for sufentanil, a μ opioid receptor selective agonist (a 1.63-fold shift), DSLET, aδ opioid receptor agonist (a 1.40-fold shift), and U50,488, a κ opioid receptor agonist (a 1.59-fold shift). Thus, NIH 10767 is devoid of significant opioid agonist or antagonist activity on the mouse *vas deferens* preparation.

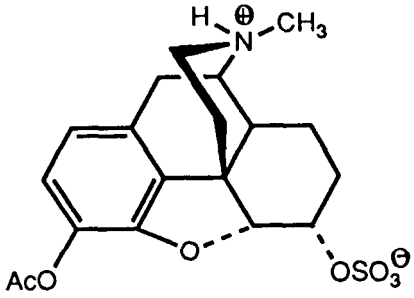
NIH 10767 (continued)

SUMMARY

NIH 10767 had no significant opioid activity activity in either preparation.

* * *

NIH 10775 Dihydromorphine 3-acetate 6-sulfate zwitterion



DISPLACEMENT OF [^{3}H]ETORPHINEBINDING

EC_{50} of 2490 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

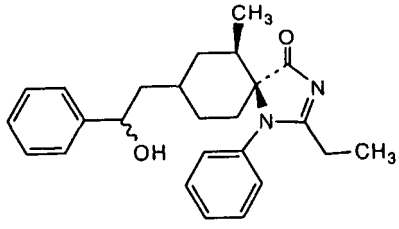
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	2404.6 ± 269.4	85.3 ± 4.2		9
Naltrexone (100 nM)	18128.0 ± 2480.9	75.3 ± 1.1	7.5	3
ICI-174,864 (100 nM)	4024.1 ± 1149.4	77.8 ± 6.3	0.9	3
Nor-BNI (10 nM)	6346.4 ± 34486.1	67.4 ± 15.0	2.6	3

SUMMARY

NIH 10775 had low potency in both assays, It was a weak partial agonist on the mouse *vas deferens* preparation. The agonist action was mediated predominantly by the μ opioid receptor. No evidence of opioid antagonist activity was found.

* * *

NIH 10788 (±)-8-(2-Hydroxy-2-phenylethyl)-2-ethyl-t-6-methyl-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-ene-r-4-one.2HCl



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 2476 nM in the presence of 150 mM NaCl.

NIH 10788 (continued)

MOUSE *VAS DEFERENS* PREPARATION

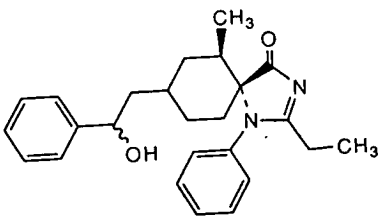
Condition	EC_{50} (μM)	Max. Response (%)	Shift (x-fold)	n
Control	3.28 ± 3.17	70.9 ± 2.2		3
Naltrexone (100 nM)	1.14 ± 1.10	66.5 ± 6.1	0.3	3

SUMMARY

NIH 10788 had low potency in the binding assay. In the mouse *vas deferens* preparation it acted as an agonist of low potency. The inhibitory effects of NIH 10788 were not antagonized by naltrexone, 100 nM. When tested as an antagonist, NIH 10788, 10 μM, did not affect responses of the *vas deferens* deferens to sufentanil (μ-opioid selective agonist), DSLET (δ-opioid selective agonist) or U50,488 (κ-opioid selective agonist). Thus, NIH 10788 appears to be devoid of significant opioid agonist or antagonist activity in the two preparations.

* * *

NIH 10789 **(±)-8-(2-Hydroxy-2-phenylethyl)-2-ethyl-c-6-methyl-1-phenyl-1,3,8-triazaspiro[4.5]dec-2-ene-r-4-one .2HCl**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 6.25 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Conditon	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	4.96 ± 1.03	98.5 ± 0.7		9
Naltrexone (100 nM)	163.6 ± 28.0	100	33.0	3
ICI-174,864 (100 nM)	9.42 ± 2.19	97.9 ± 1.3	1.9	3
Nor-BNI (10 nM)	7.61 ± 4.42	98.6 ± 1.4	1.4	3

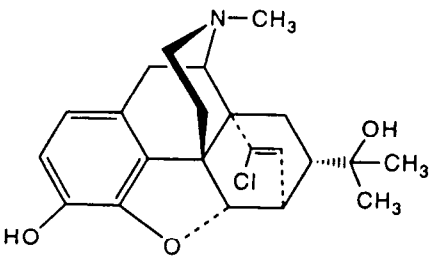
NIH 10789 (continued)

SUMMARY

NIH 10789 had high affinity in the binding assay and, in the mouse *vas deferens* preparation, it acted as an agonist with selectivity for μ opioid receptors.

* * *

NIH 10801 **18-Chloro-4,5 α-epoxy-3-hydroxy-α,α,N-trimethyl-6 α,14α-ethenoisomorphinan-7 α-methanol hydro-chloride.**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 3.73 nM in the presence of 150 mM NaCl.

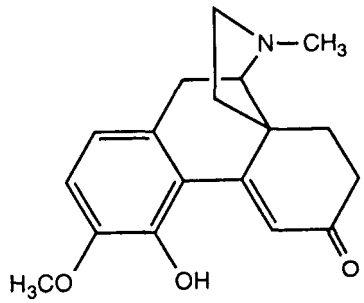
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. response (%)	Shift (x-fold)	n
Control	26.8 ± 6.5	98.9 ± 0.7		9
Naltrexone (10 nM)	809.6 ± 150.6	100	30.2	3
ICI-174,864 (100 nM)	21.6 ± 5.8	100	0.8	3
Nor-BNI (10 nM)	41.8 ± 2.5	99.4 ± 0.6	1.6	3

SUMMARY

NIH 10801 had high potency in the binding assay. In the mouse *vas deferens* preparation it acted as an agonist relatively selective for μ opioid receptors.

NIH 10804 **Metathebainone hydrochloride**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of >6,000 nM (14% inhibition at 6 μM) in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

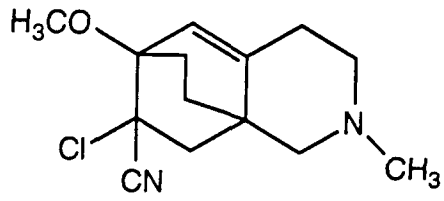
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	103.5 ± 29.6	29.6 ± 4.0		3
Naltrexone (100 nM)	347 ± 159.0	23.6 ± 6.8	3.4	3

SUMMARY

NIH 10804 had no significant activity in the binding assay. In the mouse *vas deferens* preparation it acted as a partial agonist of low potency or as a non-opioid. Naltrexone, 100 nM, only slightly antagonized the effects of this drug. When tested as an antagonist, 30 μM NIH 10804 did not affect responses of the vas deferens to sufentanil (μ opioid agonist), DSLET (δ opioid agonist) or U50,488 (κ opioid antagonist).

* * *

NIH 10817 **7-Chloro-7-cyano-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of >6000 nM (40% inhibition at 6 μM) in the presence of 150 mM NaCl.

NIH 10817 (continued)

MOUSE *VAS DEFERENS* PREPARATION

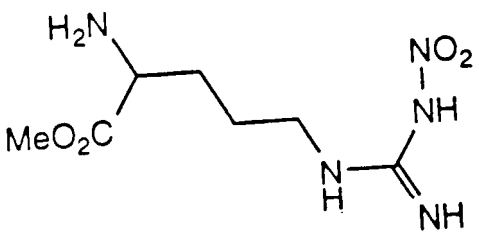
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	1.31 ± 0.32	32.7 ± 1.8		3
Naltrexone (100 nM)	1.66 ± 0.29	27.7 ± 2.5	1.3	3

SUMMARY

NIH 108 17 had low affinity in the binding assay. In concentrations of 1 nM to 10 μM, it decreased the magnitude of the twitch of the electrically-stimulated mouse *vas deferens* preparation. Naltrexone, 100 nM, did not shift the NIH 108 17 concentration effect curve. NIH 10817, 10 μM, caused a 2.89-fold shift to the right in the sufentanil concentration-effect curve. This concentration of NIH 10817 did not affect responses to either DSLET or U50,488. Thus, NIH 108 17 might have very minimal antagonist activity at μ opioid receptors at the highest concentration that was studied.

* * *

NIH 10818 Nω–Nitro-L-arginine methyl ester



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of >6000 nM (2 % inhibition at 6 μM) in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Max. Response (%)	Shift (x-fold)	n
Control	2.76 ± 0.66	80.4 ± 5.5		9
Naltrexone (100 nM)	22.0 ± 8.1	78.2 ± 7.3	8.0	3
ICI 174,864 (100 nM)	2.93 ± 0.43	66.4 ± 1.8	1.1	3
Nor-BNI (10 nM)	2.18 ± 0.19	51.7 ± 1.2	0.8	3

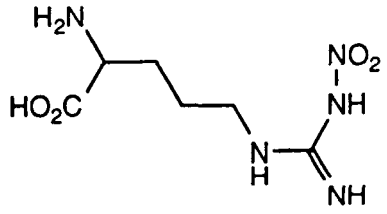
NIH 10818 (continued)

SUMMARY

NIH 10818 had a quite low affinity in the binding assay. In the electrically-stimulated mouse *vas deferens* preparation, NIH 10818 acted at high concentrations as a selective agonist for μ opioid receptors.

* * *

NIH 10819 **Nω-Nitro-L-arginine**
(N^5-[Nitroamidinol-L-2,5-diaminopentanoic acid)



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of >6000 nM (38% inhibition at 6 μM) in the presence of 150 mM NaCl.

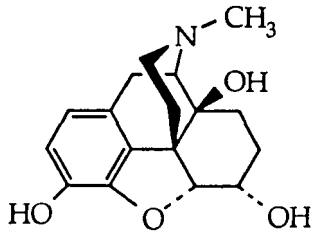
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	65.9 ± 30.9	62.8 ± 4.5		3
Naltrexone (100 nM)	46.3 ± 22.3	57.3 ± 3.7	0.7	3

SUMMARY

NIH 10819 had very low affinity in the binding assay. In the electrically-stimulated mouse *vas deferens* preparation, NIH 10819 decreased the magnitude of the twitch. Naltrexone, 100 nM, did not shift the NIH 108 19 concentration effect curve or alter the maximum response. In concentrations up to 10 μM, NIH 10819 was devoid of antagonist activity at μ, δ, and κ receptors. Thus, NIH 108 19 was devoid of significant opioid activity in either preparation.

3,6α,14-Trihydroxy-17-methyl-4,5α-epoxymorphinan



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 94 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Max. Response (%)	Shift (x-fold)	n
Control	1.03 ± 0.26	97.0 ± 1.6		9
Naltrexone (100 nM)	22.7 ± 3.2	93.9 ± 2.4	22.0	3
ICI-174,864 (100 nM)	1.73 ± 0.51	95.2 ± 3.9	1.7	3
Nor-BNI (10 nM)	0.30 ± 0.07	100.0	0.3	3

Solubility: 30 mM in 0.3 N HCl

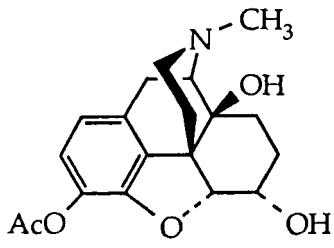
SUMMARY

NIH 10823 had high affinity in the binding preparation. In the mouse *vas deferens* deferens, it acted as a weak agonist relatively selective for μ opioid receptors.

* * *

NIH 10824

3-Acetoxy-6α,14-dihydroxy-17-methyl-4,5 α-epoxymorphinan



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 5 17 nM in the presence of NaCl.

NIH 10824 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	
Control	642.1 ± 171.2	94.0 ± 1.8		n
Naltrexone (100 nM)	23923.0 ± 4501.0	90.5 ± 8.3	37.3	9
ICI-174,864 (100 nM)	1375.4 ± 718.5	89.5 ± 3.3	2.1	3
Nor-BNI (10 nM)	704.8 ± 135.1	90.8 ± 1.5	1.1	3

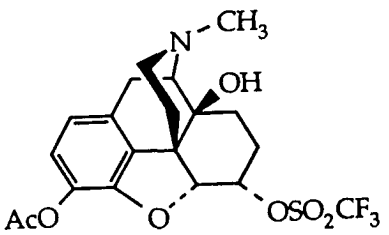
Solubility: 3 rnM in H_2O and DMSO

SUMMARY

NIH 10824 had moderate affinity in the rat brain preparation. In the mouse *vas deferens* assay, NIH 10824 acted as a partial inhibitor of the twitch, and it was relatively selective for μ opioid receptors.

* * *

NIH 10825 **3-Acetoxy-6α-trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5α-epoxymorphinan**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 1591 nM in the presence of 150 mM NaCl.

NIH 10825 (continued)

MOUSE *VAS DEFERENS* PREPARATION

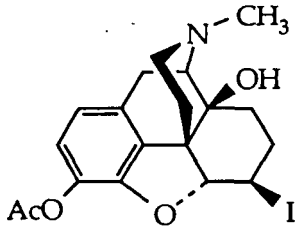
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	276.1 ± 33.3	91.3 ± 2.0		9
Naltrexone (100 nM)	6353.8 ± 763.4	52.4 ± 2.1	23.0	3
ICI-174,864 (100 nM)	664.4 ± 366.1	85.1 ± 3.8	2.4	3
Nor-BNI (10 nM)	505.3 ± 135.8	88.8 ± 2.2	1.8	3

SUMMARY

NIH 10825 had low affinity in the binding assay. In the mouse *vas deferens* preparation, it acted as a partial inhibitor of the twitch, and NIH 10825 was relatively selective for μ opioid receptors.

* * *

NIH 10826 3-Acetoxy-14-hydroxy-6 β-iodo-17-methyl-4,5 α-epoxymorphinan



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 259 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	286.7 ± 34.3	89.6 ± 2.9		9
Naltrexone (100 nM)	3265.4 ± 1443.9	84.9 ± 8.3	11.4	3
ICI-174,864 (100 nM)	462.3 ± 142.1	91.4 ± 2.0	1.6	3
Nor-BNI (10 nM)	521.5 ± 20.9	74.7 ± 2.4	2.4	3

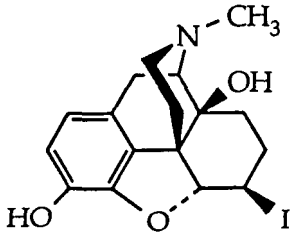
NIH 10826 (continued)

SUMMARY

NIH 10826 had moderate affinity in the binding assay. In the mouse *vas deferens* preparation, it acted as an agonist relatively selective for μ opioid receptors. The shift downward in the NIH 10826 concentration-effect curve caused by norbinaltorphimine suggests that this drug might also have some activity at the κ opioid receptor.

* * *

NIH 10827 3,14-Dihydroxy-6 β-iodo-17-methyl-4,5 α-epoxymorphinan



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 31 nM in presence of 150 mM NaCl.

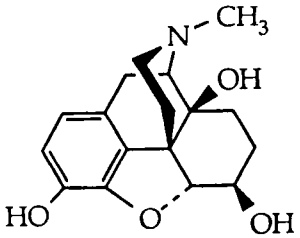
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max Response (%)	Shift (x-fold)	n
Control	62.9 ± 12.6	100.0		9
Naltrexone (100 nM)	1025.7 ± 99.1	98.1 ± 1.0	16.3	3
ICI-174,864 (100 nM)	114.4 ± 2 1.5	100.0	1.8	3
Nor-BNI (10 nM)	112.7 ± 42.8	98.5 ± 1.5	1.8	3

SUMMARY

NIH 10827 had high affinity in the binding assay. In the isolated, electrically stimulated mouse *vas deferens,* it acted as an agonist relatively selective for μ opioid receptors.

NIH 10828 **3,6β,14-Trihydrbxy-17-methyl-4,5 α-epoxymorphinnn**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 304 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

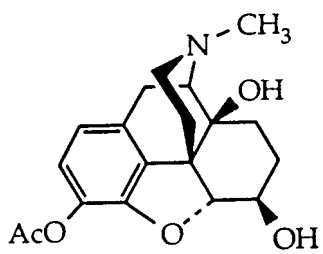
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	472.4 ± 75.5	98.2 ± 0.4		9
Naltrexone (100 nM)	7230.0 ± 745.4	89.4 ± 9.4	15.3	3
ICI 174,864 (100 nM)	408.5 ± 128.6	99.3 ± 0.7	0.9	3
Nor-BNI (10 nM)	659.2 ± 218.3	97.9 ± 0.1	1.4	3

SUMMARY

NIH 10828 had low potency in the opioid binding assay. In concentrations of 10 nM to 100 μM, NIH 10828 decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. Naltrexone (100 nM, a μ-opioid receptor antagonist) shifted the NIH 10828 concentration-effect curve to the right. Neither ICI 174864 (100 nM, aδ-opioid receptor antagonist) nor nor-binaltorphimine (10 nM, a κ--opioid receptor antagonist) shifted the NIH 10828 concentration-effect curve significantly. None of the antagonists decreased maximum responses to NIH 10828. Thus, NIH 10828 had characteristics of a μ-opioid receptor agonist.

* * *

NIH 10829 3-Acetoxy-6 β,14-dihydroxy-17-methyl-4,5 α-epoxymorphinan



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 478 nM in presence of 150 mM NaCl.

NIH 10829 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	261.3 ± 45.2	85.6 ± 2.4		9
Naltrexone (100 nM)	13520.0 ± 3423.4	76.9 ± 5.3	51.7	3
ICI 174,864 (100 nM)	275.7 ± 138.7	89.6 ± 2.3	1.1	3
Nor-BNI (10 nM)	478.5 ± 102.2	79.8 ± 2.8	1.8	3

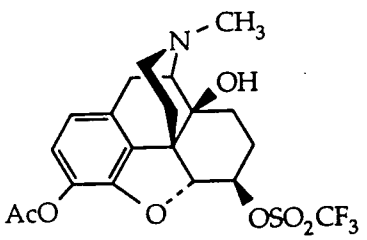
SOLUBILITY NOTE: 3 mM in 18% DMSO

SUMMARY

NIH 10829 had low potency in the opioid binding assay; In the mouse *vas deferens* preparation, in concentrations of 10 nM to 100 μM, it decreased the magnitude of the twitch. Naltrexone (100 nM) shifted the NIH 10829 concentration-effect curve to the right. Neither ICI 174864 (100 nM), a δ-opioid receptor antagonist, or the κ-opioid receptor antagonist, nor-binaltorphimine (10 nM) shifted the NIH 10829 concentration-effect curve significantly. None of the antagonists decreased maximum responses to NIH 10829. Thus, in the mouse *vas deferens* assay, NIH 10829 had characteristics typical of a μ-opioid receptor agonist.

* * *

NH3 10830 **3-Acetoxy-6 β-trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5α-epoxymorphinan**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 634 nM in the presence of 150 mM NaCl.

NIH 10830 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	2952 ± 41.1	100.0		9
Naltrexone (100 nM)	3331.8 ± 330.9	87.7 ± 4.4	11.3	3
ICI-174,864 (100 nM)	558.0 ± 148.2	94.6 ± 2.8	1.9	3
Nor-BNI (10 nM)	690.2 ± 182.4	93.7 ± 5.2	2.3	3

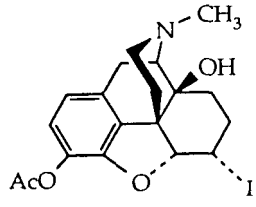
Solubility: 3 mM in H_2O and DMSO

SUMMARY

NIH 10830 acted as an agonist relatively selective for μ opioid receptors on the isolated, electrically-stimulated mouse *vas deferens* preparation. It had moderate affinity in the rat brain preparation

* * *

NIH 10831 3-Acetoxy-14-hydroxy-6 α-iodo-l7,methyl-4,5 α-epoxymorphinan



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 242 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Max. Response (%)	Shift (x-fold)	n
Control	65.3 ± 17.1	100		9
Naltrexone (100 nM)	4932.8 ± 1549.9	99.1 ± 0.9	75.6	3
ICI 174,864 (100 nM)	374.4 ± 108.7	100	5.7	3
Nor-BNI (10 nM)	28.3 ± 6.3	100	0.4	3

SOLUBILITY NOTE: 3 mM in DMSO for this assay.

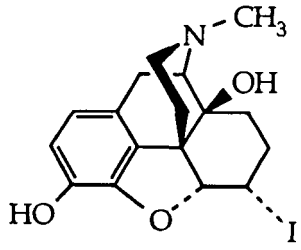
NIH 10831 (continued)

SUMMARY

NIH 1083 1 had low potency in the opioid binding assay. In the mouse vas deferens preparation, in concentrations of 1 nM to 10 μM it decreased the magnitude of the twitch. Naltrexone (100 nM) markedly shifted the NIH 1083 1 concentration-effect curve to the right. ICI 174864 (100 nM), a δ-opioid receptor antagonist, also shifted the NIH 10831 concentration effect curve to the right. The κ-opioid receptor antagonist, nor-binaltorphimine (10 nM) did not shift the NIH 1083 1 concentration-effect curve significantly. None of the antagonists decreases maximum responses to NIH 10831. Thus, in the mouse *vas deferens* assay, NIH 1083 1 had characteristics typical of both μ- and δ-opioid receptor agonists.

* * *

NIH 10832 3,14-Dihydroxy-6 α-iodo-17-methyl-4,5 α-epoxymorphinan



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 40 nM in presence of 150 mM NaCI.

MOUSE *VAS DEFERENS* PREPARATION

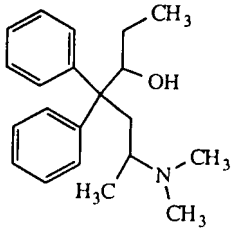
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	92.0 ± 23.7	100.0		9
Naltrexone (100 nM)	959.3 ± 493.3	100.0	10.4	3
ICI-174,864 (100 nM)	246.4 ± 136.3	100.0	2.7	3
Nor-BNI (10 nM)	58.5 ± 94.	100.0	0.6	3

Solubility: 3 mM in 0.8 N HCI

SUMMARY

NIH 10832 acted as a potent agonist in the receptor binding assay. In the isolated, electrically-stimulated mouse *vas deferens* preparation, NIH 10832 appeared to act at μ- and δ-opioid receptors.

NIH 10837 **α-(-)-6-Dimethylamino-4,4-diphenyl-3-heptanol.NCl**
(NIH 4452;α-Levomethadol, α-l-methadol)



MONKEY CORTEX BINDING

		r^2
μ-receptor:	248 nM	0.99
δ-receptor:	7% inhibition at 6 μM	---
κ-receptor:	29% inhibition at 6 μM	---

MOUSE *VAS DEFERENS* PREPARATION

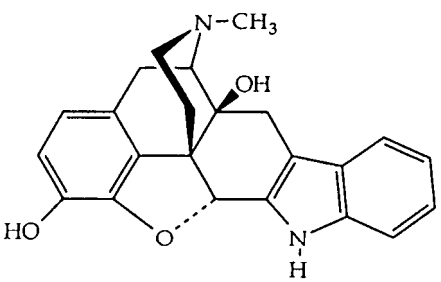
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	133.8 ± 39.6	30.9 ± 2.8		5
Naltrexone (100 nM)	54.5 ± 6.5	24.0 ± 1.3	0.4	5

SUMMARY

NIH 10837, in concentrations of 10 nM to 3 μM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. In a concentration of 10 μM, NIH 10837 was caused a slight shift to the right in the concentration effect curve for sufentanil (4.8-fold), but did not shift the curves for either DSLET (1.5-fold) or U50,488 (0.8-fold). Thus, in this assay, NIH 10837 appeared to be a weak μ opioid antagonist. In the monkey cortex binding assay it had low potency at the μ site. Thus, NIH 10837 may be a low potency, μ-selective opioid antagonist.

* * *

NIH 10842 **Oxymorphindole.HCI**



MONKEY CORTEX BINDING

		r^2
μ-receptor:	157.11	0.99
δ-receptor:	2.29	0.99
κ-receptor:	297.2	0.99

NIH 10842 (continued)

MOUSE *VAS DEFERENS* PREPARATION

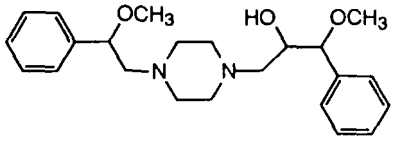
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	154.9 ± 48.6	77.9 ± 10.2		9
Naltrexone (100 nM)	333.4 ± 113.7	74.3 ± 7.5	2.2	3

SUMMARY

NIH 10842, in concentrations ranging from 10 nM to 30 μM decreased the magnitude of the twitch of the, electrically stimulated mouse *vas deferens* preparation. Naltrexone, 100 nM, caused a 2.2.-fold shift to the right in the NIH 10842 concentration-effect curve. NIH 10842, in a concentration of 100 nM, caused a slight shift to the right in the concentration-effect curve for DSLET (6.3-fold), but did not shift the concentration-effect curves for sufentanil (1.2-fold) or U50,488 (0.80-fold). Thus, in the *vas deferens* preparation, NIH 10842 appears to have some antagonistic activity at δ opioid receptors. In the monkey cortex binding assay, NIH 10842 was also selective for the δ recognition site.

* * *

NIH 10843 **Zipeprol**
[4-(2-Methoxy-2-phenylethyl)- α-(methoxyphenylmethyl)-1-piperazineethanol.2HCl]



MONKEY CORTEX BINDING

μ-receptor: 369 (305 in the absence of Na^+)
δ-receptor: No inhibition at 60 μM
κ-receptor: 67 μM

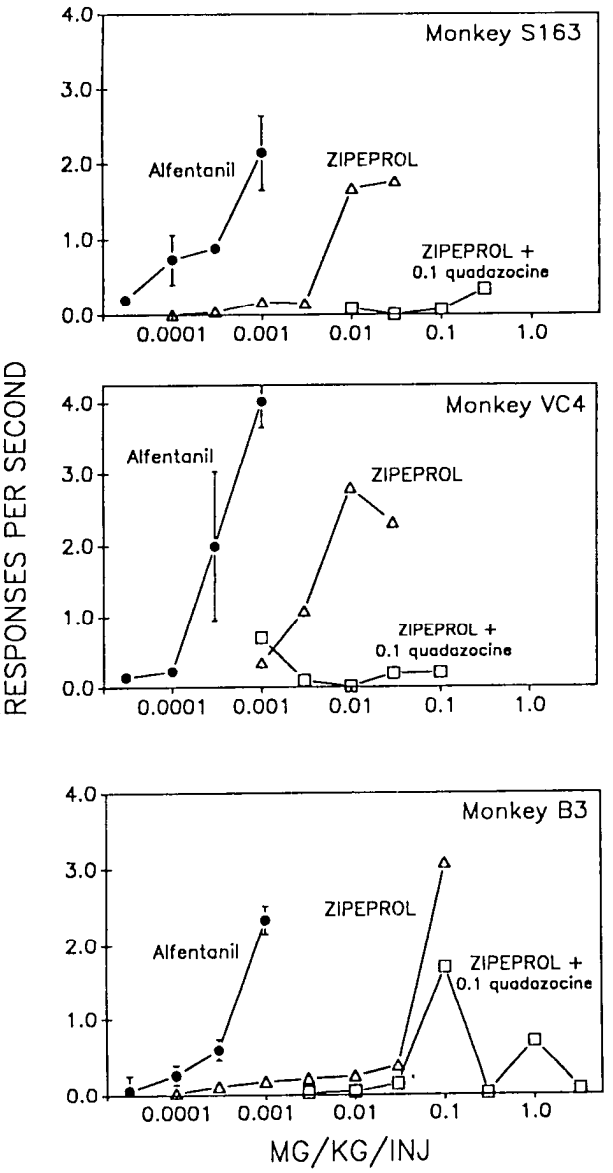
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	148.2 ± 41.3	31.9 ± 1.2		3
Naltrexone (100 nM)	54.6 ± 11.3	25.6 ± 3.8	0.4	3

NIH 10843 (continued)

SUMMARY:
***IN VITRO* PREPARATIONS**

In the monkey brain cortex binding assay, NIH 10843 displayed low potency at μ and κ binding sites without significant affinity for the δ site. In concentrations of 10 nM to 10 μM, NIH 10843 decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. Higher concentrations markedly increased the magnitude of the twitch. In this assay, NIH 10843 was a very weak antagonist at μ and κ receptors. At a concentration of 30 μM it caused a 3.2-fold shift to the right in the sufentanil concentration-effect curve and a 2.6-fold shift to the right in the U50,488 concentration-effect curve, but no shift in the DSLET concentration-effect curve. pA_2 values could not be determined because concentrations of NIH 10843 of 30 μM or greater markedly increased the magnitude of the twitch. The preparations probably are in agreement; NIH 10843 is a low potency ligand, an antagonist at μ and κ sites.



WARM-WATER TAIL-WITHDRAWAL ASSAY

NIH 10843 (1-10 mg/kg, s.c.) was more effective at 50° C than 55° C; three of four monkeys exhibited cutoff latencies at 10 mg/kg. Quadazocine (1 mg/kg, s.c.) did not alter the potency of NIH 10843. Two monkeys convulsed 10 minutes after the administration of a series of cumulative doses (1, 3, 10 mg/kg). A more gradual dose increment failed to induce convulsions.

DRUG DISCRIMINATION ASSAY: NALTREXONE

NIH 10843 (0.3-10.0 mg/kg, s.c.) was evaluated in two morphine-treated monkeys trained to discriminate naltrexone from saline. It was evaluated when morphine had been terminated for

48 hours. NIH 10843 reversed this "withdrawal response (naltrexone key selection)" at 1.0 rng/kg in one monkey. In the other monkey, naltrexone-responding continued as the choice until responding was suppressed at 10 mg/kg.

DRUG SELF-INJECTION IN ALFENTANIL-TRAINED MONKEYS

NIH 10843 was studied in three monkeys (see preceeding figure).. Each monkey self-injected NIH 10843 at doses of 0.01 - 0.1 mg/kg/inj. In each monkey NIH 10843 was less potent, but effect as a reinforcer. A dose of quadazocine (0.1 mg/kg) was given as a pretreatment. In each monkey, the reinforcing effectiveness of NIH 10843 was eliminated.

SUMMARY

NIH 10843 had both opioid and nonopioid components of activity. It produced a non-opioid analgesic effect, but it appeared to have opioid agonist activity in both the naltrexone-discrimination and alfentanil self-injection procedures. The pattern of actions seen *in vivo* are consistent with the *in vitro* preparations in illustrating NIH 10843 to have the opioid and non-opioid actions. NIH 10843 has p-agonist actions *in vivo,* and this finding is consistent with its affinity for the μ receptor binding sites.

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DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (1995)

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All compounds, except NIH 9051 (Δ^9-tetrahydrocannabinol, THC), beta funaltrexamine (BPNA), enkephalin [D-ALA^2, DLEU^5], (DPDPE), (+)- and (-)-epibatidine, and NIH 10859 (a cannabinoid receptor antagonist) were supplied by Dr. Arthur Jacobson, Laboratory of Medicinal Chemistry, NIDDK, NIH. The identities of all the compounds, except that indicated above, were unknown to us when they were originally submitted. These studies were conducted under the auspices of the Drug Evaluation Committee of the College on Problems of Drug Dependence.

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-Morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used, and they received 3 mg/kg, s.c., of morphine•SO_4 every 6 h. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. At least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 h and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-h observation period. The observer was "blind" regarding the choice of treatments. At the end of the study, the data were grouped according to dose and drug. The mean cumulative score ± SEM was calculated and the data illustrated in figure form. If indicated, the data were analyzed using the Kruskal-Wallis Anova and posthoc Mann-Whitney U-Tests.

Precipitated-Withdrawal (PPT-W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 h after the last dose of morphine. These animals were not in withdrawal. Naloxone•HCl (0.05 mg/kg, s.c.) served as the positive control.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with antagonist or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 h. Occasionally, when deemed necessary, as with cocaine, infusions were given *via* the right jugular vein.

Substitution-for-Morphine (SM) Test. The rats received morphine•SO_4 (50 mg/kg/24 h on the first day, 100 mg/kg/24 h on the second day, and 200 mg/kg/24 h from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of water. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 h at 6,24,48,72 and/or 96 h after stopping the infusion of morphine.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED50's were calculated by using computerized probit analysis. The results obtained with reference compounds are summarized in Table 1.

Tail-Flick (TF) and (TF vs M) Assays. The procedure and modifications were described (D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a slit under which was located a photoelectric cell. When the heat source of noxious stimulus was turned on, the heat focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed through the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 s under control conditions. Mice were injected with drug or vehicle and tested 20 m later. In the assay for antagonism of the antinociceptive effect, the potential antagonists were administered 10 m before the agonist, and evaluation occurred 20 m later. Table 2 summarizes our data, to date, in developing an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, delta and kappa). We chose the mouse tail-flick test and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to accommodate the fact that no delta agonist is available which is active by peripheral routes of administration.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drugs and 10 m later received 2.0 mg/kg ip of a freshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cages in groups of two each. Ten minutes after the PPQ injection, the total number of stretches per group were counted over a l-m period. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the forelimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 55°C. Mice were placed on the hot plate and activity was scored if the animal jumped or licked its paws after a delay of 5 s or more, but no more than 30 s beyond the control time.

Table 1

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick/Hot-Plate	Tail-Flick	Phenylquinone	Antagonist
Pentazocine	15% at 10.0 (12-26)	1 8 (1.0-25)	1.7	- - - -
Cyclazocine	17% at 1.0[a] (0.020-0.78)	0.03 (0.005-0.03)	0.01	____
Nalorphine•HCl	None at 10.0 (0.7-10.0)	2.6 (0.03-1.44)	0.6	____
Naloxone•HCl	None at 10.0 (0.01-0.09)	0.04	No Activity	____
Naltrexone•HCl	None at 10.0	0.007 (.002-0.02)	No Activity	____
Morphine•SO4[b]	0.7b (0.4-1.5)	Inactive	0.4[b] (0.2-0.8)	3.1[b] (1.5-6.4)
Codeine•PO4	- - - -	Inactive	- - - - (0.39-16.8)	6.4 (0.39-16.8)
Meperidine•HCl	- - - -	Inactive	- - - -	4.6 (1.8-11.7)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time
[b]ICR - Harlan-Sprague-Dawley Inc.

Calculation of Apparent pA2 Using the tail-flick assay, the apparent pA2 and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY., 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 m later by an injection of agonist. The mice were tested 30 m after receiving the antagonist. Dose-response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED50s were estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399,1949). Each dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x-l) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x-l) were plotted. The pA2 values for the antagonist were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

Table 2. Interaction of opioid agonist and antagonist subtypes in the mouse T.F. test

Antagonist s.c. or i.c.v.	Antagonist Pretreatment Time	Agonist (i.c.v.)	Agonist Pretreatment Time	ED_{50} or AD_{50} (95 % Confidence Limits)
		Morphine•SO_4-ED_{50} (MSO_4) mu agonist	10 min	ED_{50}=0.3 (0.10 to 0.90) µg/brain slope - 1.37
Naloxonazine (s.c.) 0.1 g/kg, 0.3 mg/kg or 1 mg/kg mu 1 antagonist	20 min	MSO_4-ED_{80} (1.5 µg/brain)	10 min	AD_{50}=0.27 (0.09 to .078) mg/kg slope - 2.42
		NIH 10672-ED_{50} kappa agonist	10 min	ED_{50}=0.03 (0.08 to 0.09) µg/brain slope - 1.50
NIH 10588 (s.c) 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg	1 hr 50 min	NIH 10672-ED_{80} (0.15 mg/brain) kappa agonist	10 min	AD_{50}=1.92 (0.60 to 6.12) mg/kg slope=1.50
Naloxonazine (s.c.) 0.01 m/kg, 0.03 mg/kg or 0.1 mg/kg mu 1 antagonist	20 min	NIH 10672-ED_{80} (0.15 µg/brain) kappa agonist	10 min	AD_{50}=0.05 (0.02 to 0.10) mg/kg slope = 2.54
		NIH 10815 delta agonist	10 min	15 µg/brain: 24% m.p.e. 5 µg/brain: 22% m.p.e. 1.5 µg/brain: 33% m.p.e. 0.5 µg/brain: 39% m.p.e.
		NIH 10815 delta agonist	1 hr	5 mg/brain: 0% m.p.e. 1.5mg/brain: 21% m.p.e. 0.5 mg/brain: 8% m.p.e.
		DPDPE-ED_{50} delta agonist	10 min	ED_{50} = 1.85 (0.18 TO 5.93) µg/brain SLOPE - 2.22
NIH 10589 (s.c.) 30 mg/kg, 10 mg/kg, 1 mg/kg naltrindole (delta antagonist)	1 hr 50 min	DPDPE ED_{80} 5 µg/brain delta agonist	10 min	30 mg/kg: 4 % antagonism 10 mg/kg: 8 % antagonism 1 mg/kg; 15 % antagonism

Table 2 (cont).

NIH 10589 (s.c.) 30 mg/kg, 10 mg/kg, 1 mg/kg delta antagonist	20 min	DPDPE ED_{80} 5 µg/mouse delta agonist	10 min	30 mg/kg: 0 % antagonism 10 mg/kg: 20 % antagonism 1 mg/kg; 3 % antagonism
NIH 10591 (s.c.) 30 mg/kg, 10 mg/kg 1 mg/kg N-methyl-N-nor naltrindole	20 min	DPDPE ED_{80} 5 µg/brain delta agonist	10 min	30 mg/kg: 5 % antagonism 10 mg/kg: 3 % antagonism 1 mg/kg; 0 % antagonism
		NIH 10533-ED50 U-50,488 kappa agonist	10 min	ED50- 7.2 (30.0 - 16.5) µg/brain
NIH 10588 (s.c.) (nor BNI) kappa antagonist 3 mg/kg, 1 mg/kg, 0.3 mg/kg	1 hr 50 min	NIH 10533 ED_{80} (U-50,488) kappa agonist 30 µg/brain	10 min	AD_{50} = 1.45 (0.82 to 2.58) mg/kg slope - 3.18
NIH 10588 (s.c.) (nor BNI) kappa antagonist 10 mg/kg, 3 mg/kg, 1 mg/kg	1 hr 50 min	MSO_4 ED_{80} 1.5 µg/brain	10 min	30 mg/kg: 1 % antagonism 10 mg/kg: 1 % antagonism 1 mg/kg; 8 % antagonism
NIH 10589 (s.c.) (Naltrindol) 30 mg/kg 10 mg/kg, 1 mg/kg delta antagonist	20 min	MSO_4 ED_{80} 1.5 µg/brain	10 min	30 mg/kg: 1 % antagonism 10 mg/kg: 1% antagonism 1 mg/kg; 6 % antagonism
NIH 10589 (s.c.) (Naltrindol) 30 mg/kg, 10 mg/kg, 1 mg/kg delta antagonist	1 hr 50 min	NIH 10533 ED_{80} (U-50488) 30 µg/brain kappa agonist	10 min	30 mg/kg: 15 % antagonism 10 mg/kg: 0% antagonism 1 mg/kg; 3% antagonism

Table 2 (cont).

NIH 10589 (i.c.v.) (Naltrindol) 30 µg/brain, 10 µg/brain and 1 µg/brain delta antagonist	10 min	DPDPE ED_{80} 5 µg/brain delta agonist	10 min	30 µg/brain: 0 % antagonism 10 µg/brain: 4% antagonism 1 µg/brain; 8% antagonism
I.C.I. (174,864) (i.c.v.) 30 µg/brain, 10 µg/brain and 1 µg/brain delta antagonist	10 min	DPDPE ED_{80} 5 µg/brain delta agonist	10 min	30 µg/brain: 10 % antagonism 10 µg/brain: 4% antagonism 1 µg/brain; 13% antagonism
β-FNA (i.c.v.) 10 µg/brain, 5 µg/brain, 1 µg/brain mu antagonist	4 hrs	MSO_4 ED_{50} (i.c.v.) (1.5 µg/brain)	20 min	AD_{50} = 4.22 (1.37 to 13.02) mg/brain slope - 1.33
β-FNA (i.c.v.) 10 µg/brain mu antagonist	4 hrs	DPDPE ED_{80} (i.c.v.) 5 µg/brain	20 min	10 µg/brain: 59% antagonism
β-FNA (i.c.v.) 10 µg/brain mu antagonist	4 hrs	NIH 10672 ED_{80} (s.c.) 0.1 mg/kg	20 min	10 µg/brain: 5% antagonism
I.C.I. 174864 (i.c.v.) 3 µg/brain, 1 µg/brain delta antagonist	20 min	DPDPE ED_{80} (i.c.v.) 5 µg/brain	20 min	3 µg/brain: 0% antagonism 1 µg/brain: 0% antagonism
I.C.I. 174864 (i.c.v.) 3 µg/brain, 1 µg/brain delta antagonist	10 min	DPDPE ED_{80} (i.c.v.) 5 µg/brain	10 min	3 µg/brain: 33% antagonism 1 µg/brain: 19% antagonism
NIH 10589 (Naltrindol) 30 µg/brain, 20 µg/brain, 10 µg/brain	Same as Agonist	DPDPE ED_{80} 10 µg/brain delta agonist	10 min	AD_{50} = 19.64 µg/brain 12.47 to 30.90 Slope - 4.04

There are a number of interesting points made by perusal of this data. First, we can obtain good agonist data using the icv route for relatively specific mu (morphine), kappa (NIH 10672 and U-50.488) and delta (DPDPE) ligands. The delta agonist NIH 10851 was not active as an analgesic. As to antagonists, the "specific" mu compound naloxonazine was considerably more potent as a kappa than as a mu antagonist when given subcutaneously. This was a surprising finding.

Summary (cont)

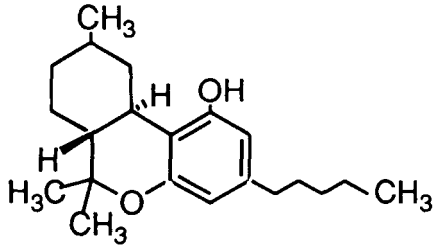
The kappa antagonist NIH 10588 (nor-BNI) was fully effective subcutaneously against both kappa agonists but not effective against morphine. Naltrindole (NIH 10589). the purported delta antagonist was active versus DPDPE when given concomitantly with DPDPE. It was also ineffective against mu and kappa agonists. ICI 174,864 another purported delta antagonist, was inactive versus DPDPE, β-FNA, another specific mu antagonist, given i.c.v. was effective against morphine but inactive versus both kappa and delta agonists.

Table 3. Apparent pA_2 values[a] using the mouse tail-flick assay

Treatment Antagonist/Agonist	Schild Plot pA_2 (95% C.L.) Slope	Constrained Plot pA_2 (95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1-7.6)
2) Nalmefene/Morphine	8.0 (7.6 - 8.3)-1.1	8.0 (7.7 - 7.6)
3) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
4) (-)-Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 -0 7.6)
5) Naloxone/Sufentanil	7.0 (6.9 - 7.1)-1.0	7.0 (6.9 - 7.0)
6) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
7) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-0.7	7.2 (6.9 - 7.5)
8) Naloxone (-)-Nicotine	5.3 (5.3-5.3)-0.5	7.0 (6.9 - 7.0)
9) Naloxone/U-50,488	6.6 (6.3 - 6.9)-1.1	7.2 (6.9 - 7.5)
kappa agonist		6.6 (6.3 - 7.0)
10) Naloxone /NIH 10672	6.1 (5.6 - 6.6)-1.2	6.2 (5.9 - 7.3)
selective kappa agonist		
11) (-)-Quadazocine/NIH 10672	6.2 (6.1 - 6.2)-1.7	6.7 (6.6 - 6.8)
12) nor BNI/NIH 10672	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
13) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	6.5 (6.4 - 6.6)

[a]Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA_2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significantly from unity, this may indicate non-equilibrium conditions, interactions with multireceptors, receptor sensitization, precoupling mechanisms, or multiple drug properties. With a constrained plot, the slope of the regression line is restricted to slope = -1.

NIH 9051 (-)-Δ^{9}-tetrahydrocannabinol (THC)



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF 4.7 (2.3 - 9.7)[a,b]
2) PPQ - 0.3 (0.1 - 0.8)[a,b]
   a) Intravenously
   b) Vehicle - ethanol: emulphor: sterile saline; 1: 1: 18)

Special: SR141716A[c,d] (i.p.) antagonism of THC ED_{50} (i.v.) in TF -AD_{50} = 1.4 (0.8 - 2.4) versus THC ED_{50} (i.v.) in PPQ assay AD_{50} - 1.0 (0.3 - 3.9)

c) N-(piperidin-1-yl)-5-(4chlorophenyl)-1-(2,4-chlorophenyl)-4-methyl-1H pyrazole-3-carboxamide•HCl) a purported THC antagonist (Rinaldi-Carmona et al., FEB. Letters, 350, 240-244, 1994).
d) Vehicle - ethanol: emulphor: sterile saline; 1: 1: 18

Comment:

SR141716A effectively blocks THC-induced antinociception in the TF and PPQ assays. The results support the view that SR14176A is a selective THC antagonist.

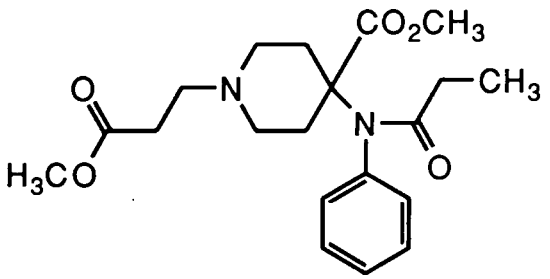
RAT CONTINUOUS INFUSION ASSAY

Δ^{9} -Tetrahydrocannabinol (THC)-precipitated withdrawal,

The controversial question of physical dependence on THC, a psychoactive cannabinoid was addressed using SR141716A. a selective antagonist (see above for chemical formula and reference). Unanesthetized male Sprague-Dawley rats previously fitted with intraperitoneal cannulas (Teiger, J. Pharmacol. Exp. Ther., 1974) were infused continuously with Δ^{9}-tetrahydrocannabnol (THC).

Dose regimens of 12.5 or 2.5 or 0.5 mg/kg/ on day 1, 1.25 or 5 or 1 mg/kg on day 2,50 or 10 or 2 mg/kg on day 3 and 100 or 20 or 4 mg/kg on day 4, respectively were administered. The rats were challenged with SR141716A (10 mg/kg i.p.) and observed. Within 10 m, an intense dose-related behavioral syndrome characterized mainly by the signs wet-dog shakes, face rubbing and tongue rolling was noted. Any one of these signs occurred at the rate of at least 1 per m in the rats receiving the highest dose of THC. The syndrome subsided in 1 hr. These results provide strong evidence that Δ^{9}-THC produces physical dependence and that SR141716A is a selective antagonist. For other information regarding the effects of SR14171A in morphine-dependent monkeys, see NIH 10859.

NIH 10747 3-(4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]piperidine)propanoic acid, methyl ester hydrochloride or N-Phenyl-N-[1-(2-methoxycarbonylethyl)-4-methoxycarbonyl-4-piperidinyl]-propanamide hydrochloride]



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

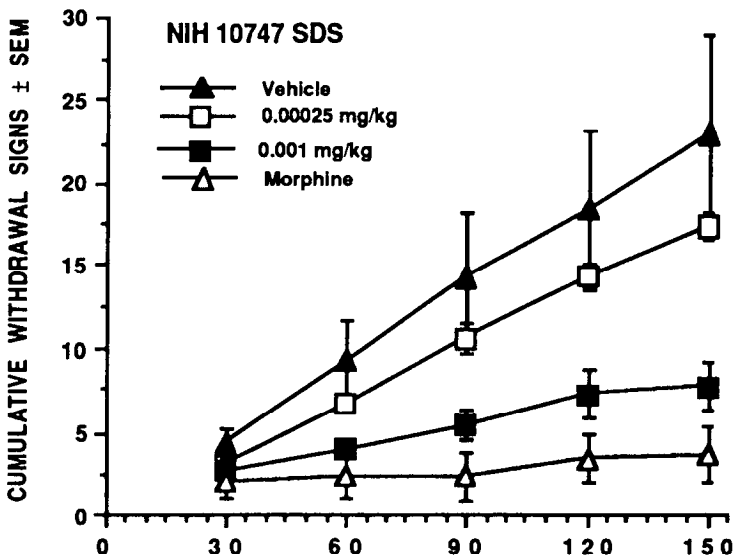
1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - Inactive at 1.0 and 10.0, 19% at 30.0[a]
4) HP - 13% at 1.0, 10.0 and 30.0[a]

[a]Increased locomotion and Straub tail at 30.0
No longer present at 20 min.
Naloxone blocked these effects at 0.1 mg/kg.

MONKEY DATA

(SDS)

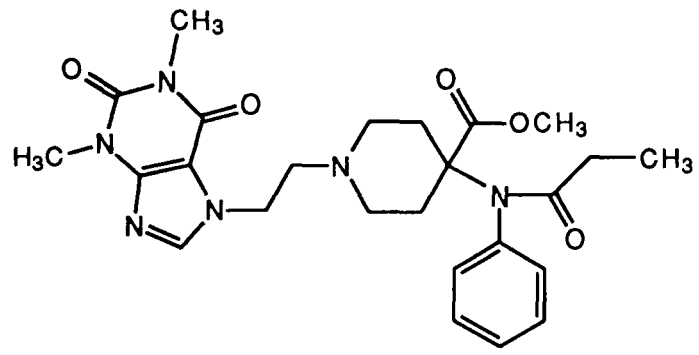
Although 10747 dose-dependently attenuated withdrawal (see fig.), some signs designated restlessness, wet-dog shakes and retching were never completely extinguished. Onset of action was immediate and offset was like that of the reference compound morphine. Potency estimated at 3000 x morphine.



In a preliminary assay, a monkey receiving 1.0 mg/kg collapsed and stopped breathing within 2 m after receiving the drug. Naloxone and artificial respiration reversed these effects. The monkey recovered completely.

Comments: In the mouse, NIH 10747 behaved as a typical mu agonist for the first 10 m. But no antinociceptive action was present at 20 m. Perhaps, the drug was rapidly metabolized. Some atypical attenuation of withdrawal was noted in the monkey, but overall, the drug appeared to be a mu agonist.

NIH 10764 N-PhenyI-N-[1-(2-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7**H**-purin-7yl)ethyl)-4-methoxy-carbony-piperidinyl]propanamide oxalate

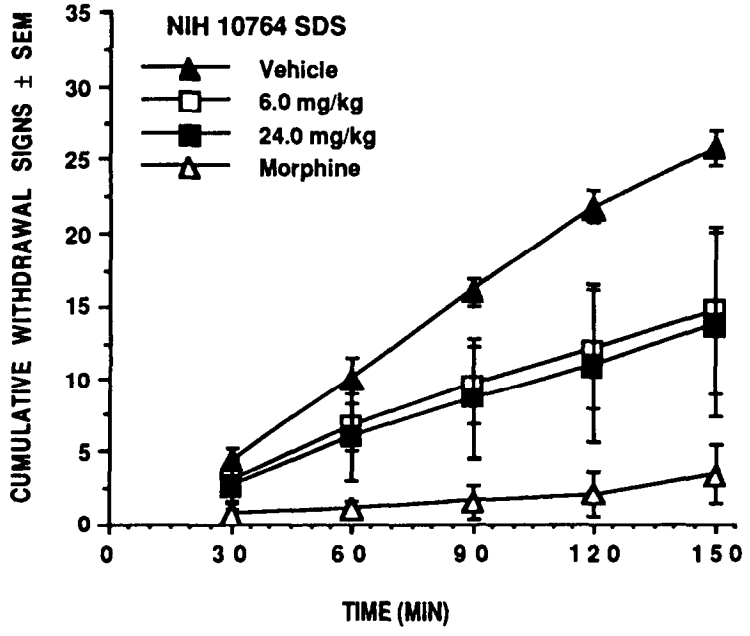


MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

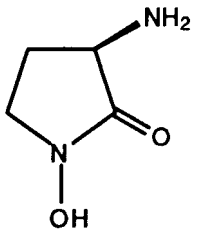
1) TF - 8% at 1.0 and 3.0, 29% at 10.0 and 38% at 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 17% at 1.0, 29% at 10.0 and 54% at 30.0
4) HP - Inactive at 1.0 and 10.0, 15% at 30.0

MONKEY DATA
SDS

NIH 10764 did not substitute completely for morphine at doses of 6 and 24 mg/kg (see fig.) The drug attenuated withdrawal and appeared to decrease the incidence of the signs designated wet-dogs, rigid abdomen and vocalization when abdomen palpated.



NIH 10767 *R*-(+)-3-Amino-1-hydroxy-2-pynolidone



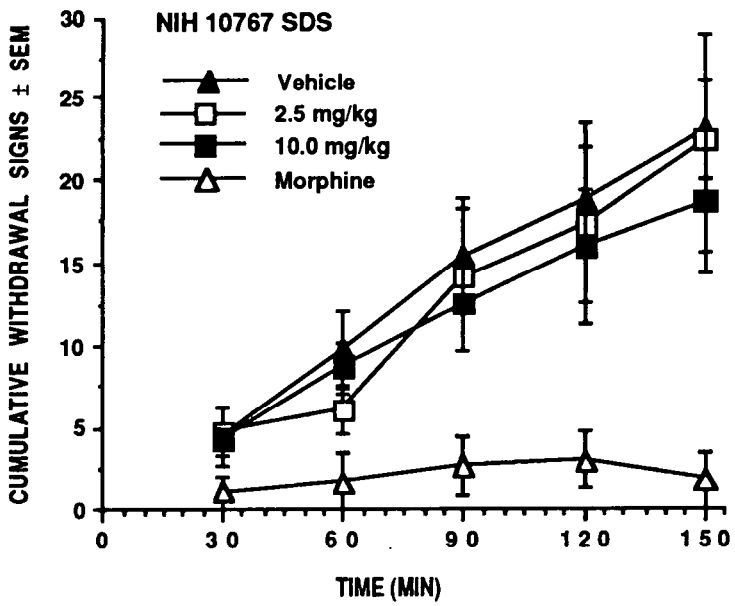
MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 1.8 (0.5 - 7.3)
4) HP Inactive at 1.0, 10.0 and 30.0

Special Test: Naloxone produced 14% antagonism of PPQ ED80 at 1.0 mg/kg.

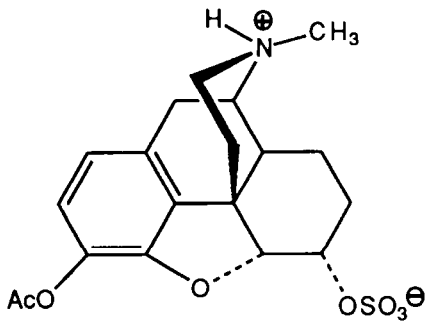
MONKEY DATA
SDS

As shown in the accompanying figure, NIH 10767 at doses of 2.5 and 10.0 mg/kg neither substituted for morphine nor exacerbated withdrawal. The vehicle consisted of one drop of hydrochloric acid and water. The number of subjects was 3 animals per treatment regimen except at the high dose, in which case, 5 monkeys were used.



Comment: NIH 10767 appears to have very few, if any, opioid effects.

NIH 10775 Dihydromorphine 3-acetate 6-sulfate zwitterion

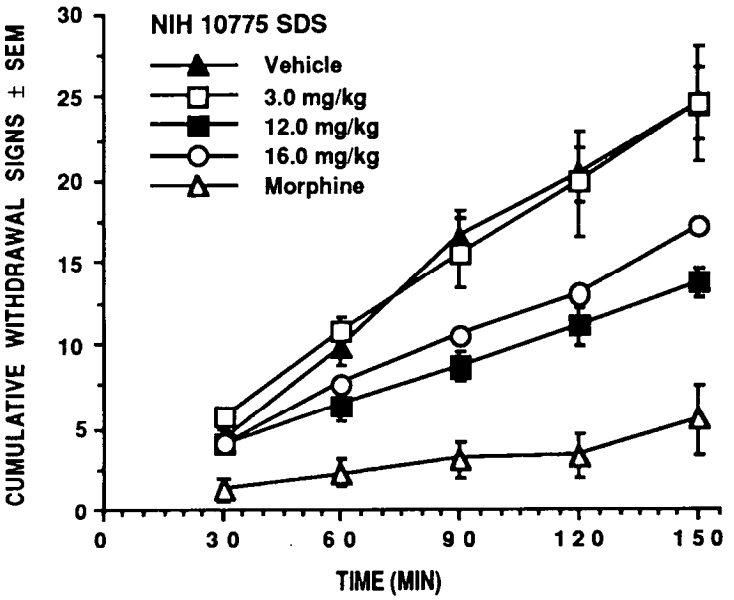


MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 4.2 (1.6 - 11.1)
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.7 (0.3 - 1.6)
4) HP - 5.0 (3.5 - 7.3)[b]

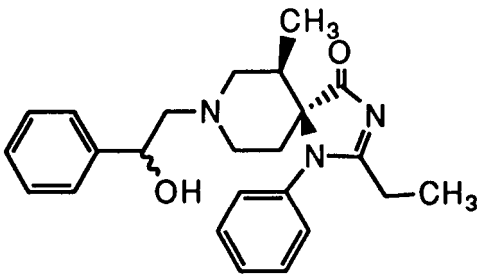
MONKEY DATA
SDS

Although there was an overall, inconsistent dose-response attenuation of withdrawal signs (see fig.), NIH 10775 did not substitute for morphine nor did it exacerbate withdrawal.



Comment: The mouse and monkey data are not in accord regarding selective mu-agonist profiles of activity. However, certain kappa agonists will display a similar antinociceptive profile

NIH 10788 (±)-2-hydroxy-2-phenylethyl-2-ethyl-t--6methyl-1-phenyl-1-1,3,8-triazaspiro[4,5]dec-2-ene-r-4-one•HC1

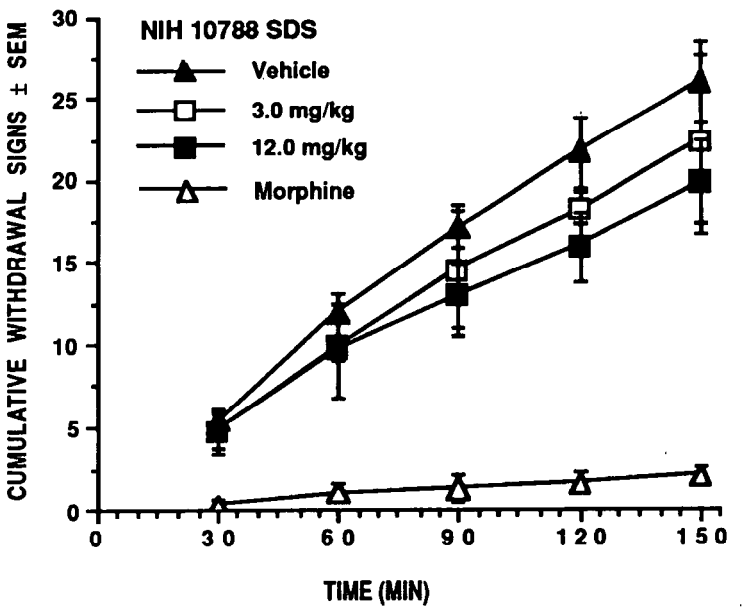


MOUSE DATA-ED50 or AD50
(95% CL.) or % change (mg/kg)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - 1.0. 10.0 and 30.0
3) PPQ - 12% at 1.0 and 10.0, 43% at 30.0
4) HP - 25% at 0.03 and 0.1; 13% at 1.0 and 10.0 and 25% at 30.0

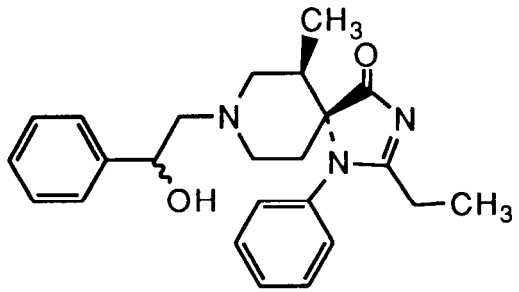
MONKEY DATA
SDS

In the dose range of 3.0 - 12.0 mg/kg, NIH 10788 neither substituted for morphine nor exacerbated withdrawal. At the high dose, some delayed suppression of withdrawal signs was noted.



Comment: The results suggest that this compound lacks significant opioid activity. Perhaps onset of action is delayed.

NIH 10789 (±)-2-Hydroxy-2-phenylethyl-2ethyl-c-6-methyl-1-phenyl-1-1,3,8-tri-azaspiro[4,5]dec-2ene-r-4-one•HCl



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

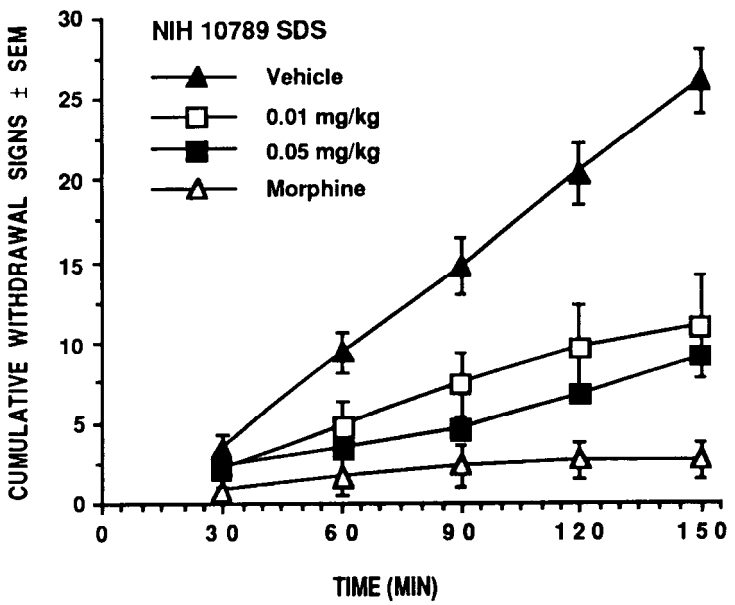
1) TF - 0.011 (0.005 - 0.027)[a]
2) TF vs. M - Inactive at 1.0. 10.0 and 30.0[b]
3) PPQ - 0.003 (0.001
4) HP - 0.051 (0.031 - 0.084)[c]

[a]Straub tail at 0.1
[b]Straub tail and increase locomotor activity at 1.0
[c]Straub tail at 0.1

Special: Naloxone AD50 vs ED80 of NIH 10789 in TF- 0.024 (0.006 - 0.092)

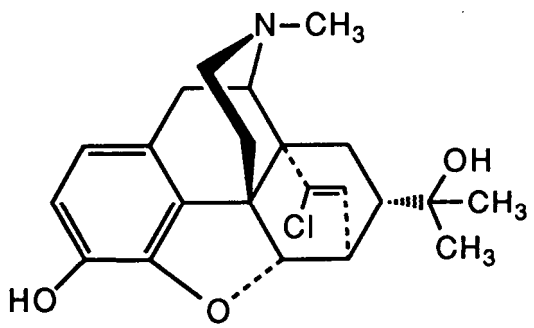
MONKEY DATA
(SDS)

As shown in the fig., at doses of 0.01 and 0.05 mg/kg, NIH 10789 dose-dependently substituted completely for morphine. However, although the drug acts promptly, the duration of action is short (about 60-75 m). Potency estimate is approximately 60 x morphine.



Comment: The mouse and monkey data suggest that NIH 10789 has significant mu agonist activity.

NIH 10801 18-Chloro-4,5α-epoxy-3-hydro-α,α,N-trimethyl-6α,14α-etheneoisomorphinian-7α-methanol hydrochloride



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 0.03 (0.009 - 0.1)
2) TF vs. M - Inactive at 1.0. 10.0 and 30.0
3) PPQ - 0.01 (0.004 - 0.015)
4) HP - 0.03 (0.01 - 0.09)

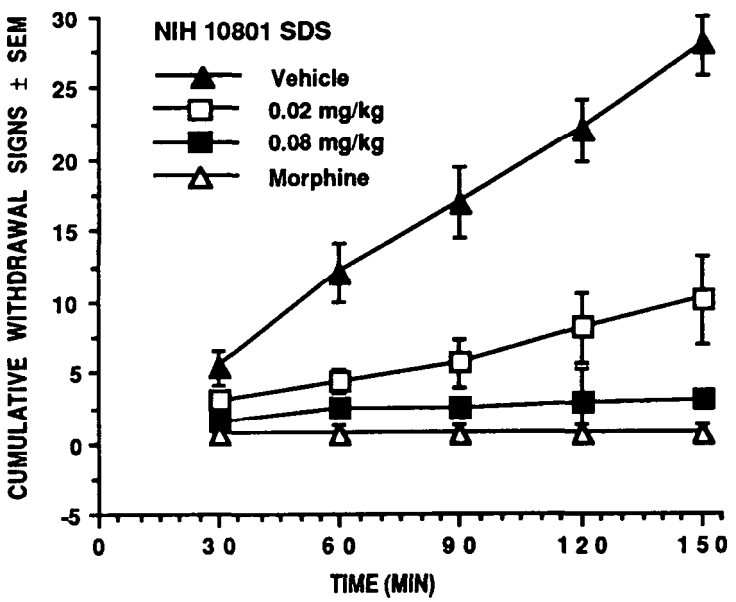
5) Special Test: Naloxone AD50 vs ED80 of NIH 10801 in TF - 0.3 (0.1 - 0.5)

MONKEY DATA
SDS

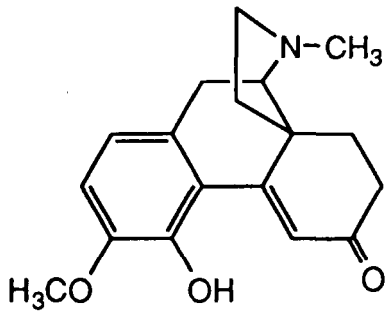
As shown in the graph, NIH 10801 dose-dependently substituted completely or morphine; however, this was accompanied at the high dose by the signs sagging, slowing, ataxia and scratching. Onset was prompt and offset was less than that of morphine. Potency estimate is 150 x morphine.

Comment:

In addition to the obvious mu opioid profile, the relatively high AD50 value in the special naloxone-antagonist study in the mouse hints at kappa activity.



NIH 10804 Metathebainone hydrochloride

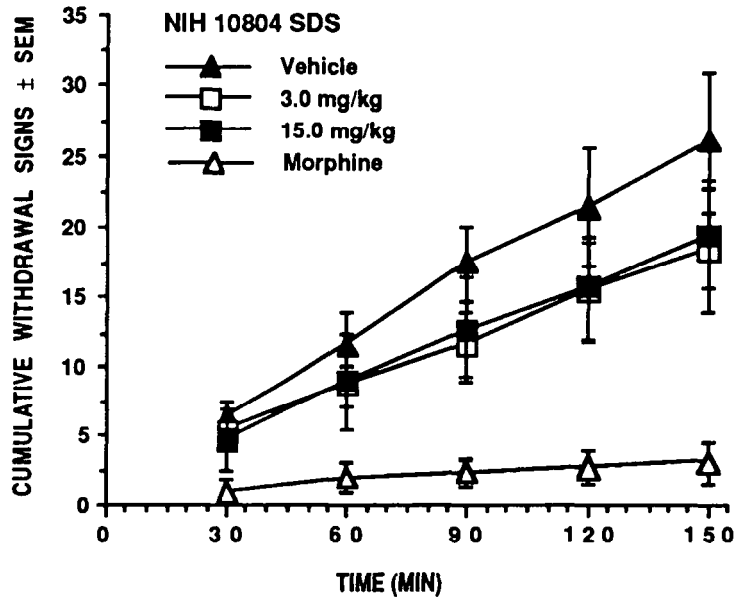


MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 18% at 30.0, Inactive at 1.0 and 10.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 14% at 1.0, 17% at 10.0 and 29% at 30.0
4) HP - Inactive at 1.0, 10.0 and 30.0

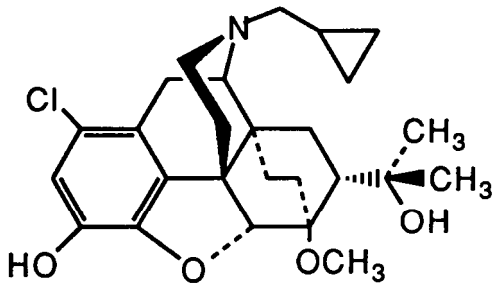
MONKEY DATA
SDS

This compound (NIH 10804) neither substituted for morphine nor exacerbated withdrawal (see accompanying fig.). Two monkeys, one at each dose, were standing quietly at times and appeared "almost" cataleptic. This may account for the apparent reduction in scores as illustrated in the figure. Some chewing not associated with food was noted in a monkey receiving the high dose.



Summary: NIH 10804 is devoid of significant antinociceptive activity and has little effect in morphine-dependent monkeys. Some overt behavioral signs in monkeys suggested dopaminergic (D_2) blockade.

NIH 10805 1-Chlorodiprenorphine oxalate

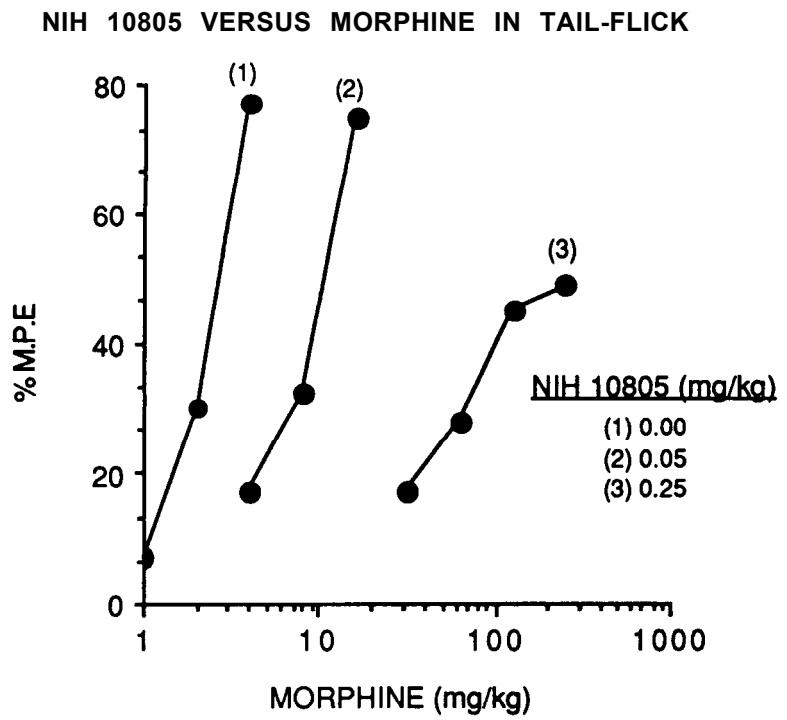


MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - 0.09 (0.03 - 0.3)
3) PPQ - Inactive at 1.0, 10.0 and 14% at 30.0
4) HP - Inactive at 1.0, 10.0 and 25% at 30.0

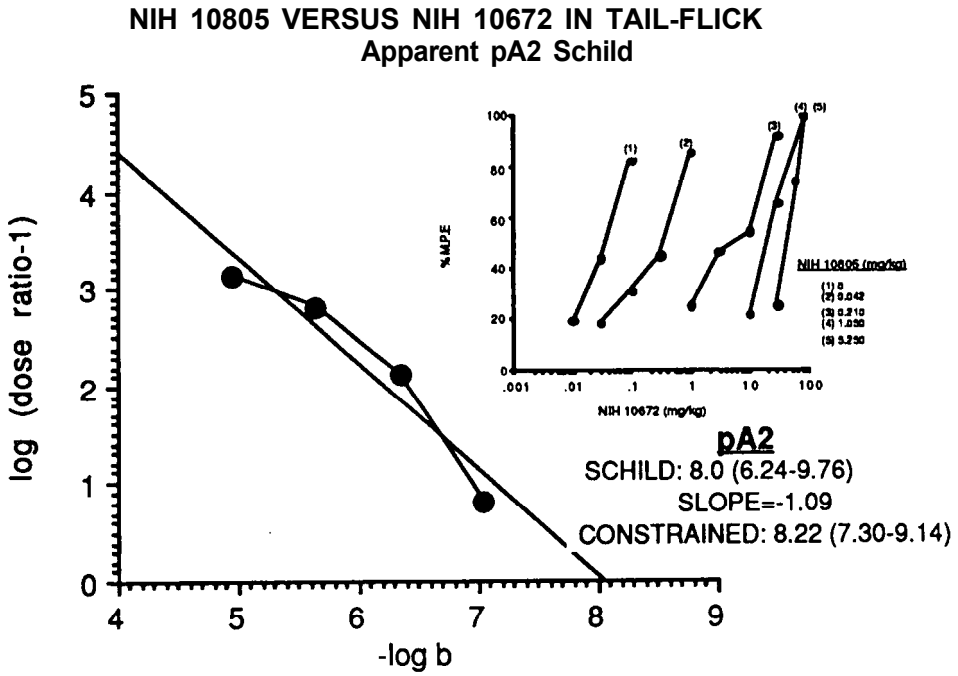
5) Apparent pA_2 vs Morphine (mu agonist) in Tail-Flick Test

As shown in the fig., NIH 10805 behaved as a non-competitive antagonist,



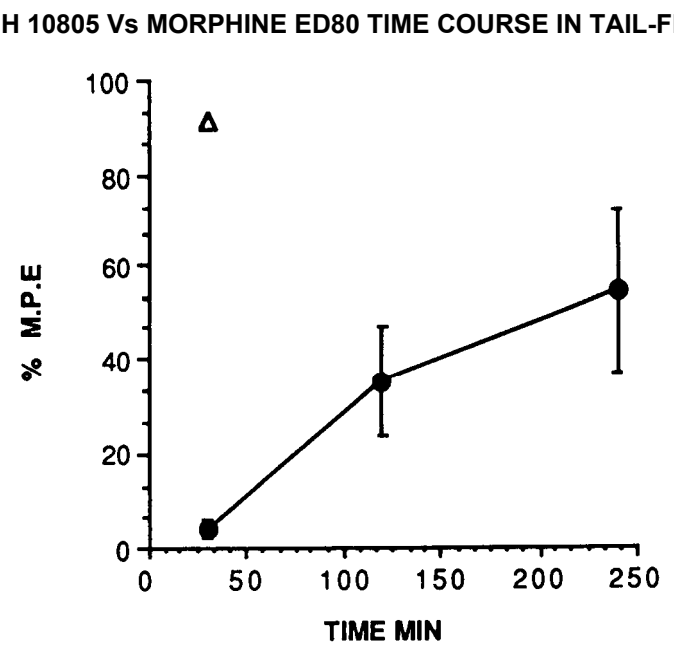
4) Apparent pA_2 vs NIH 10672 (kappa agonist) in Tail-Flick Test

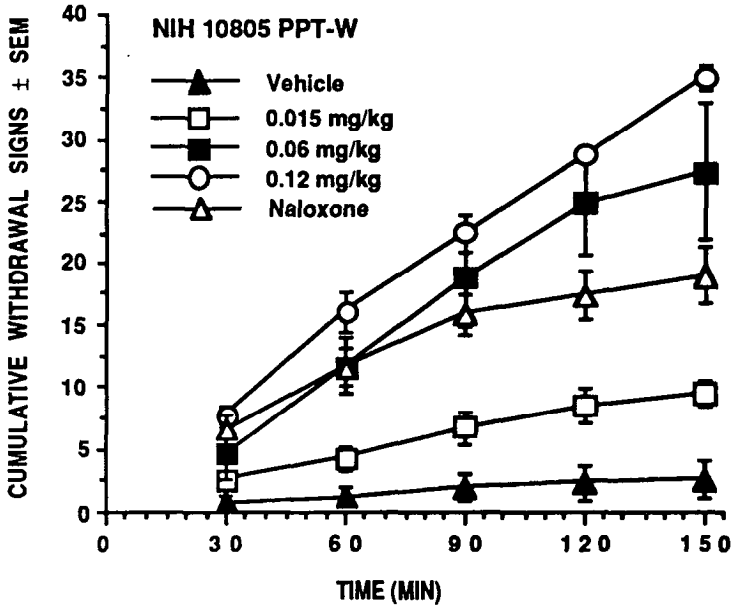
An apparent pA_2 of 8.0 was calculated for NIH 10805 (see accompanying fig.). The results indicate that NIH 10805 has a high affinity for the kappa receptor.



5) Special Time-Course Study vs ED80 of morphine in Tail-Flick

The results illustrated in the fig. suggest that NH 10805 acts promptly and has a duration of action in excess of 4 h.





MONKEY

1) Preliminary SDS

At doses of 0.01, 0.02 mg/kg at 15 m intervals respectively, NIH 10805 exacerbated withdrawal, Two 3.0 mg/kg doses of morphine were not completely effective in attenuating withdrawal.

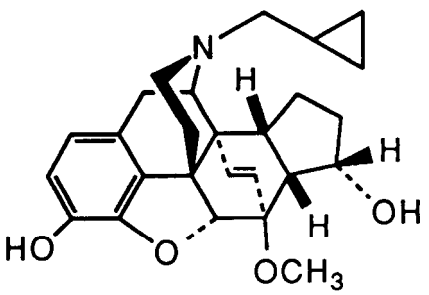
2) PPt-W

NIH 10805 dose-dependently precipitated withdrawal in morphine-dependent monkeys. Onset and duration of action are similar to those of naloxone at equipotent doses. In addition, potency is estimated to be equivalent to that of naloxone. At the highest dose tested, some of the monkeys defecated, showed body jerks, ejaculated semen frequently and uttered clucking noises.

Comments:

NIH 10805 is a potent opioid antagonist with an unusual combination of mechanisms in the mouse; it behaved as a noncompetitive antagonist on mu receptors and as a competitive antagonist on kappa receptors. In monkey studies, NIH 10805 has mu antagonist properties.

NIH 10810 N-Cyclopropylmethyl[7 α,8α,2'3']cyclopentano-1'-[S]hydroxy-6- 14-endoethenotetrahydro nororipavine hydrochloride•HCl

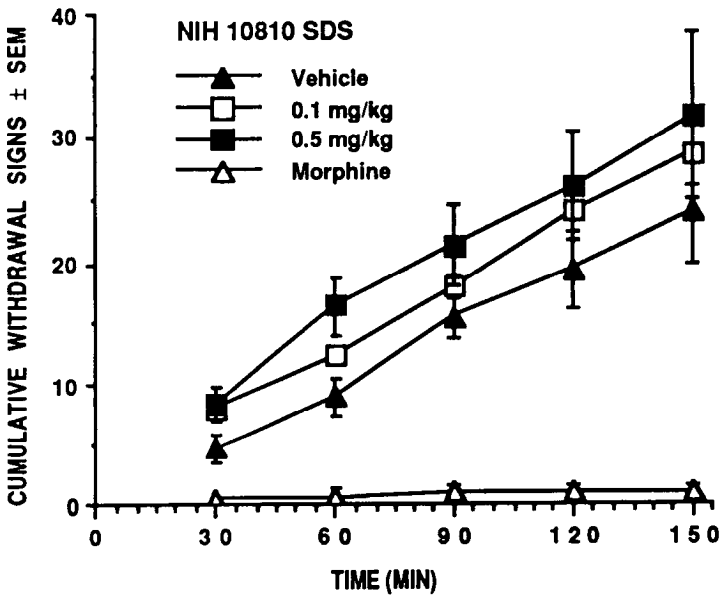


MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

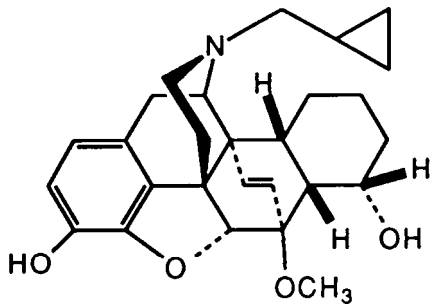
1) TF - 8% at 1.0, 16% at 10.0 and 3% at 30.0
2) TF vs. M - 0.4 (0.2 -1.3)
3) PPQ - 3% at 1.0, 6% at 10.0 and 11% at 30.0
4) HP - 0% at 1.0, 13% at 10.0 and 0% at 30.0

MONKEY DATA
SDS

NIH 10810 neither substituted for morphine nor suppressed withdrawal. Instead, withdrawal was exacerbated. The drug acted promptly and the duration of action was longer than that of naloxone. a reference standard used in this laboratory. The drug appears to have 1/10 the potency of naloxone.



NIH 10811 N-Cyclopropylmethyl-[7 α,8α ,2',3']cyclohexano-1'[S]-hydroxyd,14-endoetbenotetrahydronororipavine hydrochloride



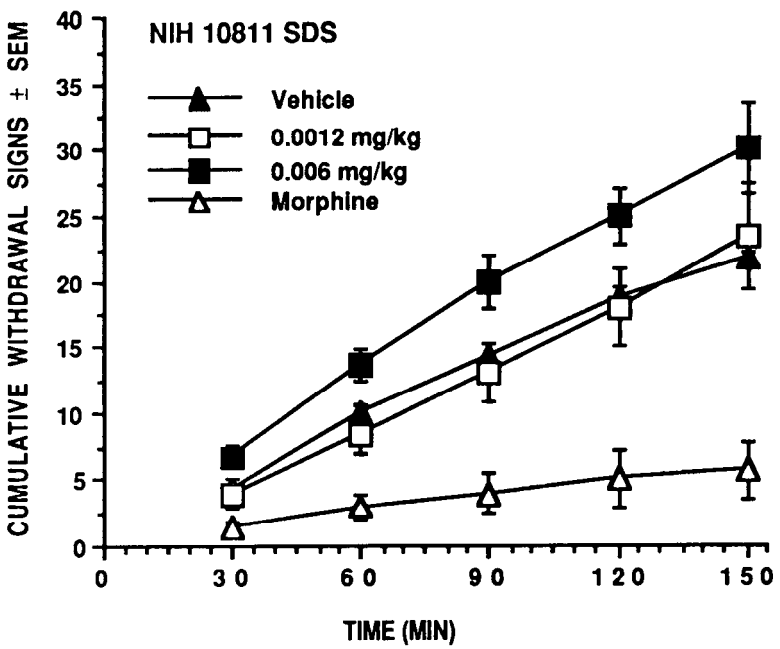
MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 10% at 1.0, 9% at 10.0 and 12% at 30.0
2) TF vs. M - 0.02 (0.01 - 0.06)
3) PPQ - 9% at 1.0, 3% at 10.0 and 11% at 30.0
4) HP - Inactive at 1.0 and 10.0, 13% at 30.0

MONKEY DATA

A. SDS

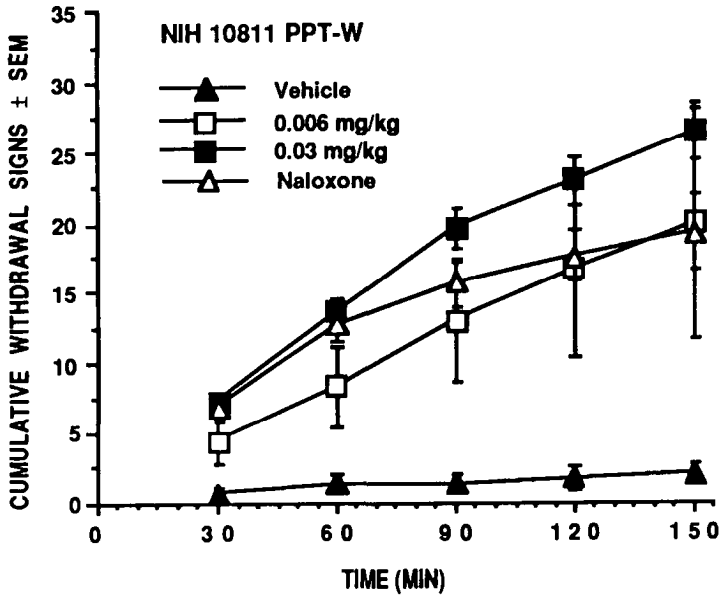
As shown in the graph, NIH 10811 neither suppressed withdrawal nor substituted for morphine. However, the drug exacerbated withdrawal. Onset was prompt and offset was at least 2 1/2 hr.



B. PPt-w

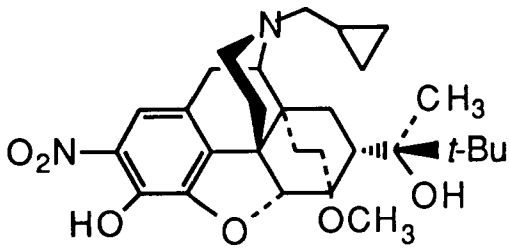
NIH 10811 produced a dose-related precipitated withdrawal (see fig.). Onset was fast and duration of action was at least twice as long as the reference standard naloxone. Potency estimate is 5 x that of naloxone.

NIH 10811 (continued)



Comment:

NIH 10812 2-Nitrobuprenorphine hydrochloride



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 20% at 1.0, 23% at 10.0 and 4% at 30.0[a]
4) HP - Inactive at 1.0, 10.0 and 30.0[a]

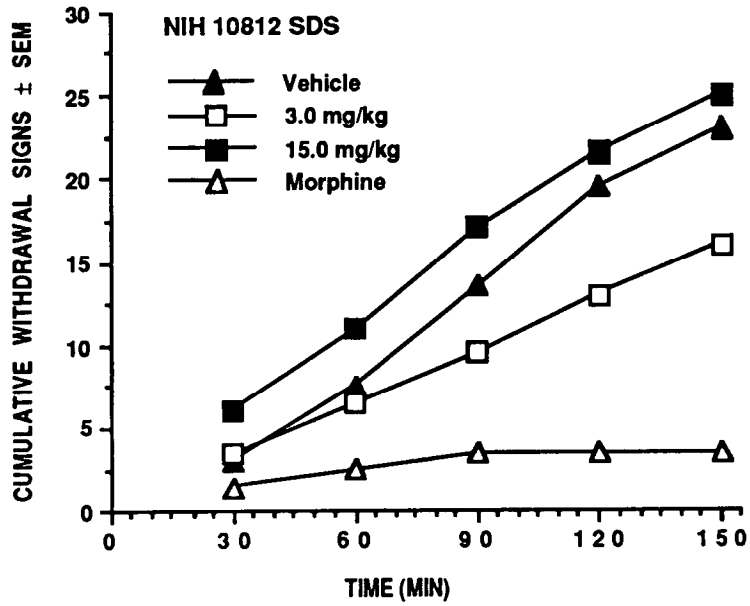
[a]Vehicle 1 drop lactic acid and water

MONKEY DATA

(SDS)

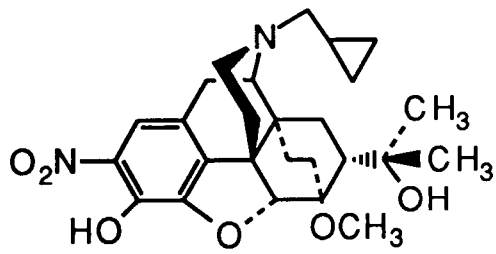
Because of limited supplies, the number of subjects per treatment regimen was 2. On the basis of these results (see fig.), it is tentatively concluded that NIH 10812 neither substituted for morphine nor exacerbated withdrawal. Vehicle was 25% hydroxypropyl-β-cyclodextrin in water. Drug solution had a deep orange color.

NIH 10812 (continued)



Comment: NIH 10812 does not appear to have remarkable opioid properties.

NIH 10813 2-Nitrodiprenorphine hydrochloride



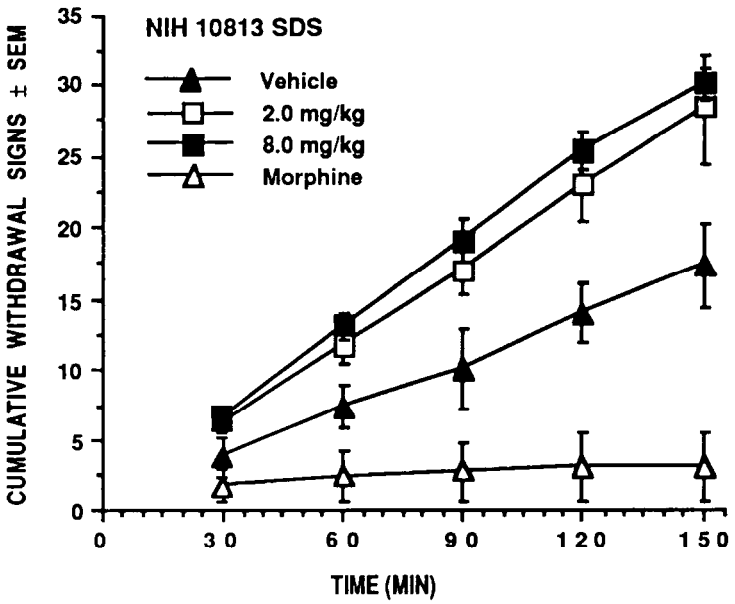
MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 7% at 1.0, 3% at 10.0 and 11% at 30.0
2) TF vs. M - 0% at 1.0, 19% at 10.0 and 27% at 30.0
3) PPQ - 11% at 1.0, 17% at 10.0 and 29% at 30.0
4) HP - 13% a 1.0, 10.0 and 30.0.

MONKEY DATA
(SDS)

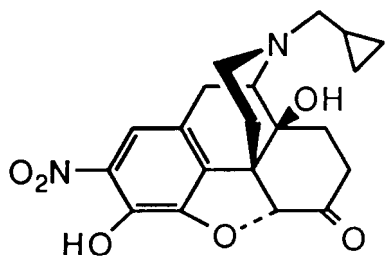
NIH 10813 did not substitute for morphine; it may have exacerbated withdrawal. It should be noted that the exacerbation may be more apparent than real because the vehicle controls had much lower than normal cumulative withdrawal scores. The solution was slightly cloudy and had a fruity odor.

NIH 10813 (continued)



Comment: NIH 10813 appears to have weak, if any, opioid antagonist properties.

NIH 10814 2-Nitronaltrexone hydrochloride



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 4.3 (2.2 - 8.3)[a]
2) TF vs. M - 3.8 (1.7 - 8.2)
3) PPQ - 1.2 (0.5 - 2.9)
4) HP - 0% at 1.0, 13% at 3.0 and 25% at 30.0

[a]Convulsant at 10.0

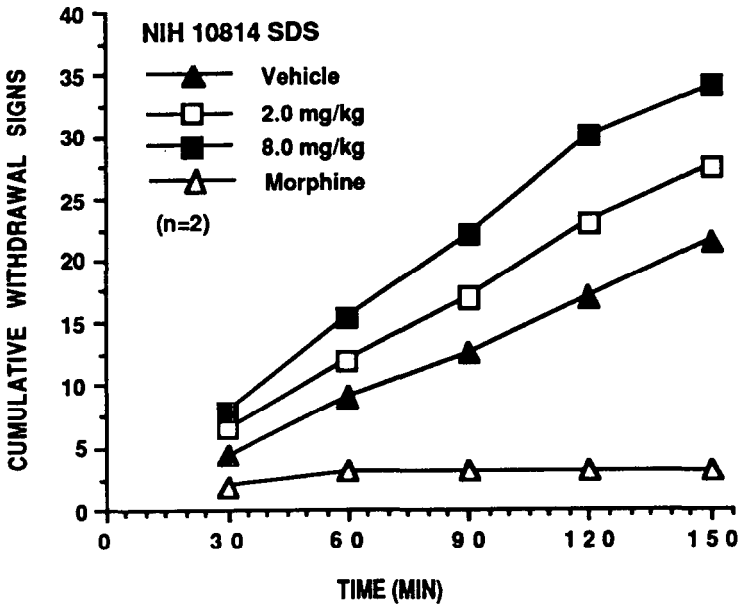
Special test: Naloxone AD50 vs ED80 of NIH 10814 in TP = 2.2 (1.0 - 4.7)

MONKEY DATA

(SDS)

As shown in the fig., NIH 10814 exacerbated withdrawal in a dose-related manner. One monkey receiving the high dose developed severe tremors, myoclonic jerks and began gasping for breath. The experiment with that group was terminated so that the stricken monkey could receive medical attention. However, the monkey died within 15 m. This accounts for an n of 2 per treatment regimen.

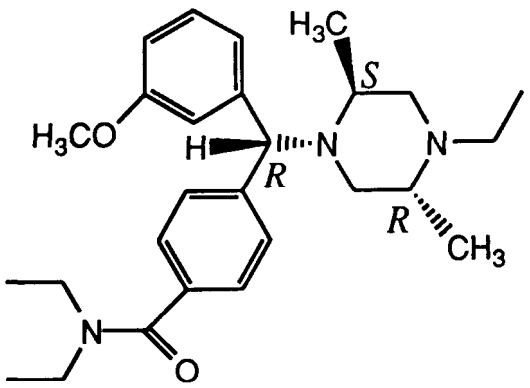
NIH 10814 (continued)



Flexor muscles were stiff 15 m after the monkey ceased breathing.

Comment: The results with mice and monkeys show mu antagonist activity. However, a strong convulsant component was manifested in both species.

NIH 10815 (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-NN-diethylbenzamide



MOUSE DATA-ED50 or AD50
(95% CL.) or % change (mg/kg)

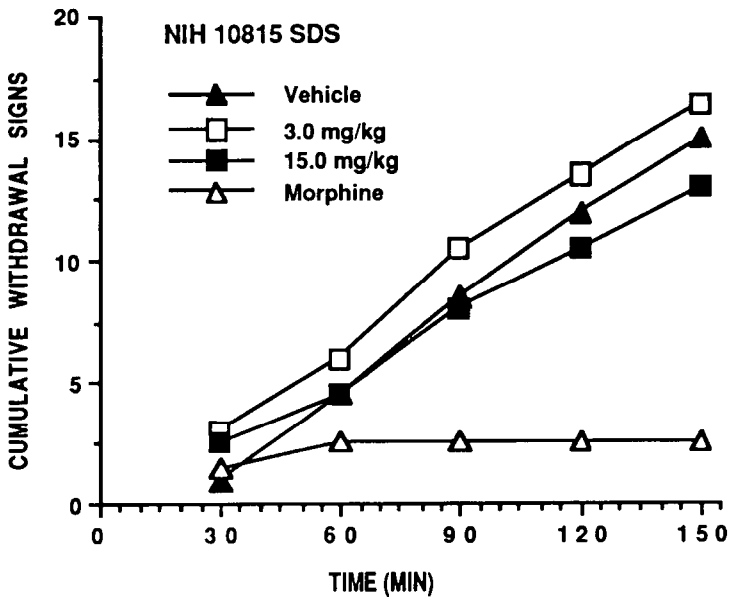
1) TF - Inactive at 1.0 and 10.0, 27% at 30.0
2) TF vs. M - Inactive at 1.0 and 10.0. 15 % at 30.0
3) PPQ - 3.8 (1.6 - 9.3)
4) HP -Inactive at 1.0, 10.0 and 30.0

NIH 10815 (continued)

MONKEY DATA

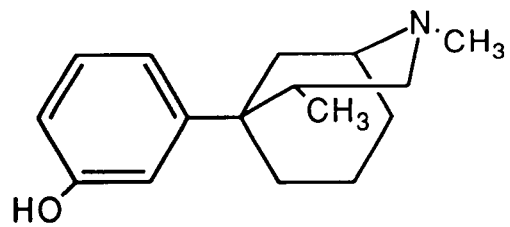
(SDS)

Due to limited supplies of NIH 10815, only 2 subjects per treatment regimen were tested. The results are illustrated in the accompanying graph. Based on these results, it is concluded that this compound neither suppressed nor exacerbated withdrawal. Ataxia and slowing were observed in monkeys receiving NIH 10815.



Comment: NIH 10815 does not display a profile of activity consistent with opioid activity.

NIH 10816 (±)-2,4-Dimethyl-5-(3-hydroxyphenyl)morphan•HBr



1) TF - 0% at 1.0 12% at 10.0 and 39% at 30.0
2) TF vs M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 15.8 (7.2 - 35.1)
4) HP - Inactive at 1.0 and 10.0, 13% at 30.0

NIH 108 16 (continued)

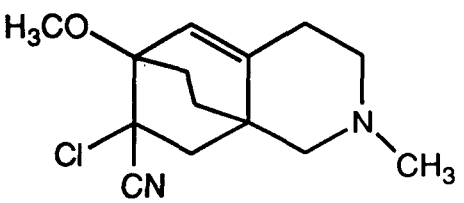
Monkey
(Preliminary SDS)

One monkey received doses of 0.5, 1, 2, 4 and 7.5 mg/kg in the sequence indicated at 15-m intervals. The compound did not suppress withdrawal signs. Instead, tremors, chewing and increased respiratory rate were noted. Drug supply was exhausted.

Comment

NIH 10816 appears to be free of mu agonist properties. The behavioral signs suggest increased CNS activity and/or weak antagonist properties.

NIH 10817 7-Chloro-7-cyano-1,2,3.4,6,7,8,8 α-octahydro-6-methoxy-2-methyl 6,8a-ethanoisoquinoline



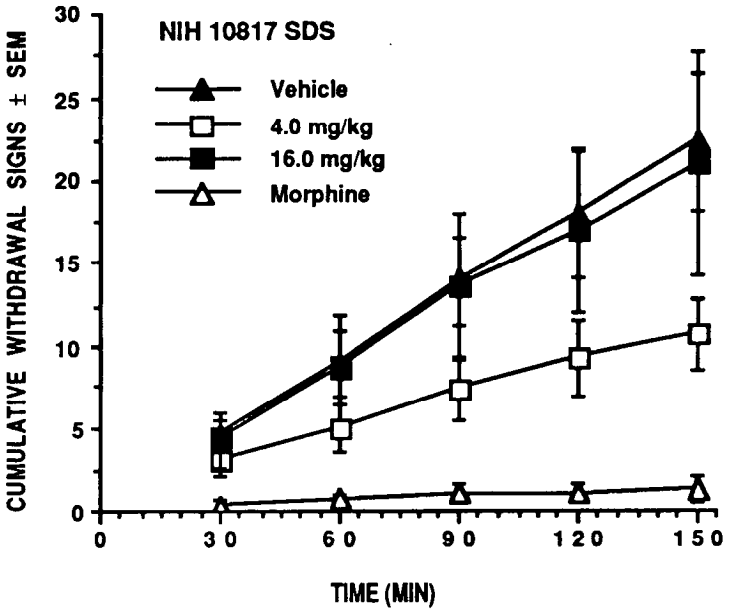
MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - Inactive at 1.0 and 10.0, 54% at 30.0[a,b]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 11% at 1.0, 29% at 10.0 and 60% at 30.0[a]
4) HP - Inactive at 1.0, 10.0 and 30.0[a]

[a]Vehicle 1 drop lactic acid and water
[b]Mice moved about slowly at 30.0

MONKEY DATA
(SDS)

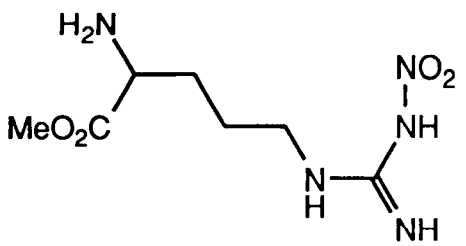
As can be seen in the accompanying figure, NIH 10817 suppressed partly, the withdrawal syndrome at the low dose and had no apparent effect at the high dose. Most of the suppression was due to a reduction in the signs designated vocalizes when abdomen palpated, abdominal muscle rigidity and retching. At the high, dose the signs termed chewing and stiff tail, in 2 monkeys and aggressive behavior in 1 monkey were observed.



Comments

The profile of activity in mice suggested weak antinociceptive activity possibly associated with opioid activity. The results in monkeys supported this interpretation at the low dose. However, at the high dose, stimulant properties may have emerged, possibly of dopaminergic origin.

NIH 10818 N-ω-Nitro-L-arginine methyl ester



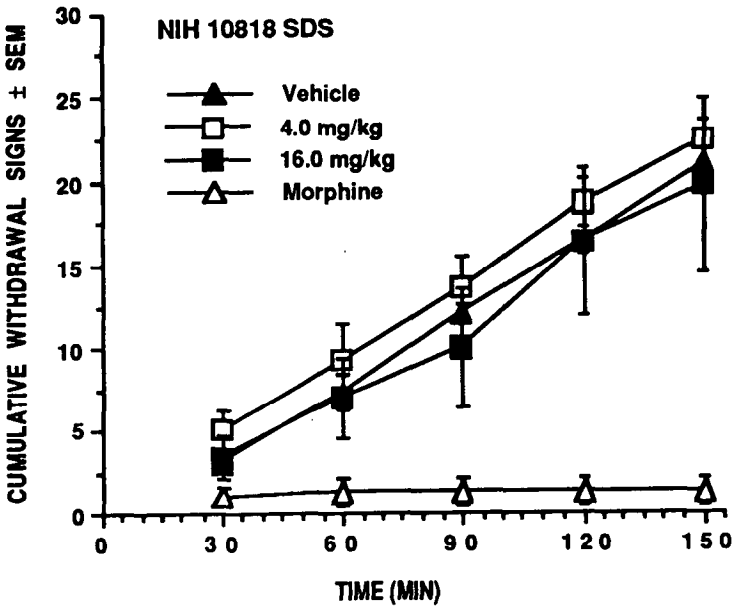
MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - Inactive at 1.0, 10.0 and 30.0
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 14% at 1.0 and 30.0, 11% at 10.0
4) HP - 13% at 30.0, Inactive at 1.0 and 10.0

NIH 10818 (continued)

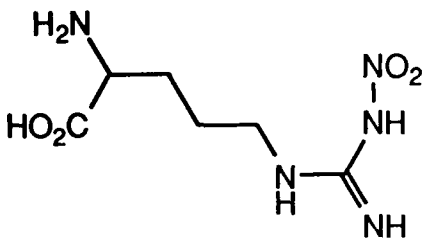
MONKEY DATA
(SDS)

NIH 10818 neither substituted for morphine nor exacerbated withdrawal (see fig.). At the highest dose, one monkey was standing quietly and respiration appeared depressed. Another monkey seemed confused and was also sitting quietly or occasionally lying on its side.



Summary: Although overt behavioral signs were observed in monkeys, NIH 10818 does not display remarkable mu agonist or antagonist activity.

NIH 10819 N-ω-Nitro-L-arginine (N^5-[Nitroamidino]-L-2,5-diaminopentanoic acid)



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 17% at 30.0, Inactive at 1.0 and 10.0[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - Inactive at 1.0, 20% at 10 and 34% at 30.0[a]
4) HP -25% at 30.0, Inactive at 1.0 and 10.0[a]

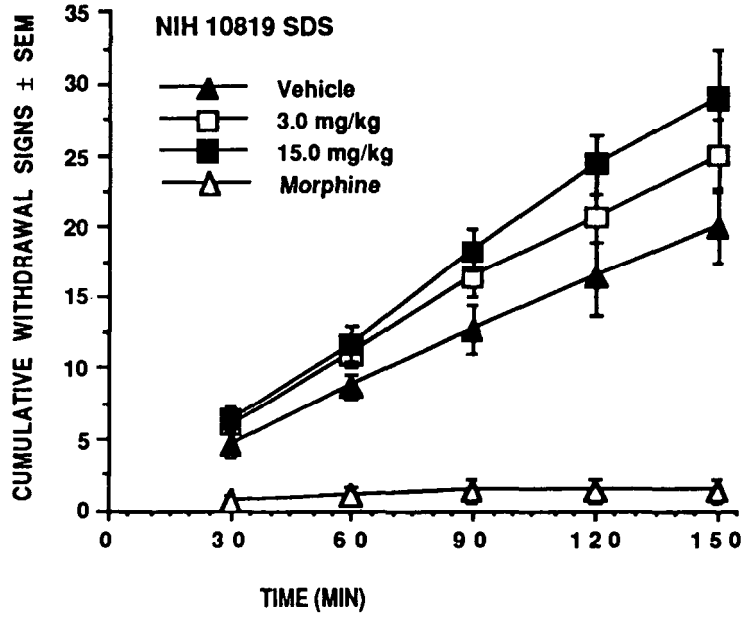
[a]Vehicle-dil HCl and H_2O

NIH 10819 (continued)

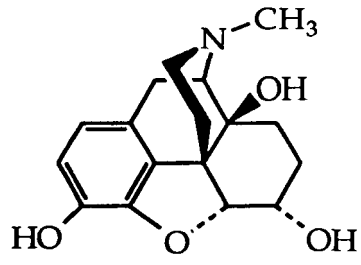
MONKEY DATA
(SDS)

As shown in the fig., NIH 10819 did not substitute for morphine and may have exacerbated withdrawal. Two monkeys receiving the 15 mg/kg dose vomited. This sign is not usually seen during abrupt withdrawal providing some evidence that the drug may have mu antagonist activity.

Summary: All in all, NIH 10819 does not display significant opioid (mu) agonist activity. However, in the monkey, there are indications that it has opioid antagonist properties.



NIH 10823 3,6α,14-Trihydroxy-17-methyl-4,5 α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 0.4 (0.2 - 0.9)[a]
2) TF vs M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.11 (0.04 - 0.26)[a]
4) HP - 1.2 (0.5 - 2.8)[a]

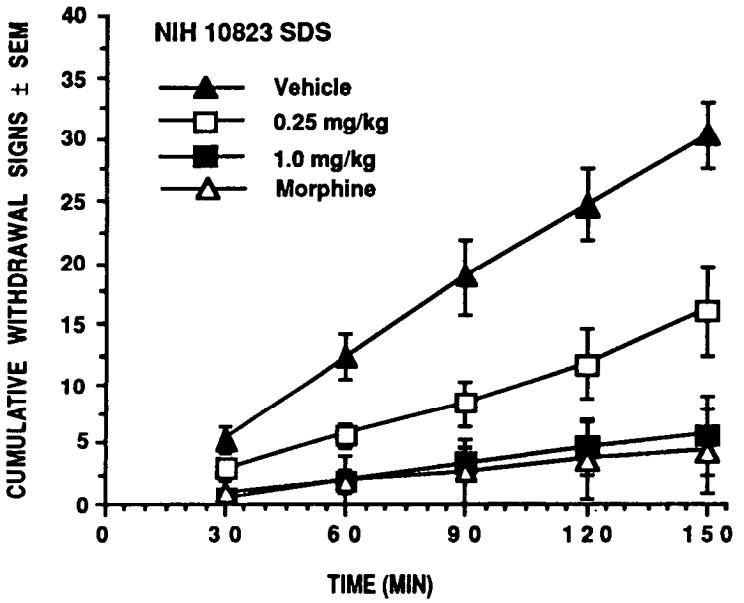
[a]Vehicle•HCl and water

Naloxone vs ED_{80} of NIH 10823 in TF = AD_{50} 0.07 (0.03 - 0.16)

NIH 10823 (continued)

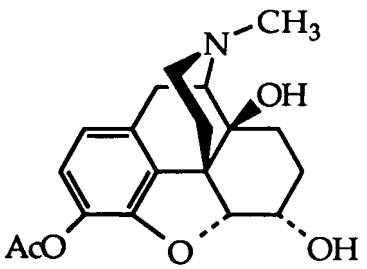
MONKEY DATA
SDS

At doses of 0.25 and 1 mg/kg, NIH 10823 dose-dependently substituted for morphine. Onset and offset of action were similar to those of the reference standard, morphine. Potency estimate is 3 x that of morphine•SO_4.



Commentary: NIH 10823 and morphine share the same profile of activity.

NIH 10824 3-Acetoxy-6α,14-dihydroxy-17-methy1-4,5α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% CL.) or % change (mg/kg)

1) TF - 0.3 (0.1 - 0.8)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.14 (0.05 - 0.35)[a]
4) HP - 0.61 (0.20 - 1.81)[b,c]

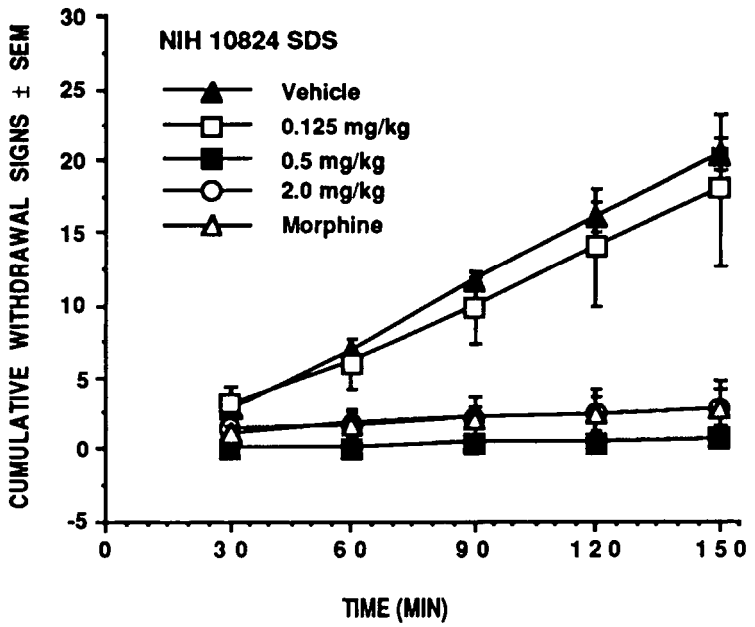
[a]Vehicle - 5% hydroxypropyl--cyclodexhin in H_2O
[b]Vehicle - lactic acid and H_2O
[c]Straub test and locomotor stimulation

Naloxone vs ED_{80} of NIH 10824 in TF, AD_{50} = 0.025 (0.007 - 0.09)

NIH 10824 (continued)

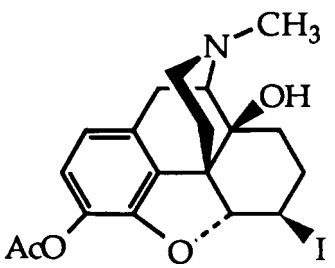
MONKEY
(SDS)

As shown in the figure, NIH 10824 substituted completely for morphine at 0.5 and 2.0 mg/kg. Onset and duration of action are similar to morphines. Potency estimate is 10 x morphine•SO_4. Vehicle was 10% hydroxypropyl-β-cyclodextrin in H_2O.



Overview: The profile of activity suggests a compound with mu-agonist properties.

NIH 10826 3-Acetoxy-14-hydroxy-6iβ-iodo-17-methyl-4,5α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 0.02 (0.01 - 0.05)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.02 (0.01 - 0.02)[a]
4) HP - 0.03 (0.02 - 0.07)[a]

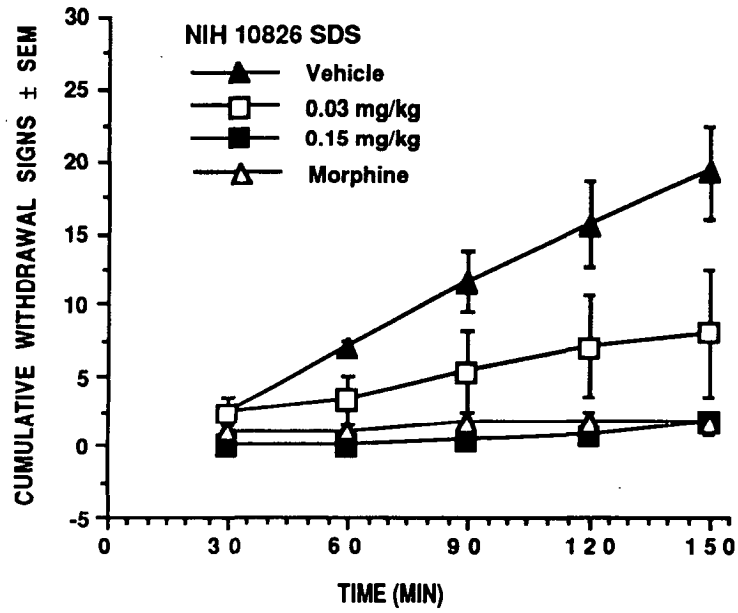
[a]Vehicle - lactic acid (1 gutta) in water

NIH 10826 (continued)

MONKEY DATA

(SDS)

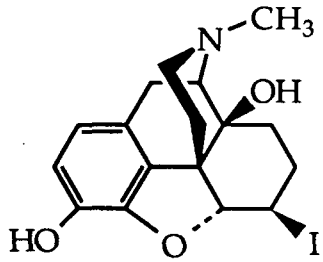
As depicted in the fig., NIH 10826 dose-dependently attenuated withdrawal at doses of 0.03 and 0.15 mg/kg. Onset and offset of action were similar to morphine's Potency estimate is 20 x morphine. Vehicle was dil HCl in 10% hydroxypropyl-β--cyclodextrin. pH of solution was 5.5.



Commentary

The profile of activity is suggestive of a typical mu agonist.

NIH 10827 3,14-Dihydroxy-6β-iodo-17-methyl-4,5α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 0.04 (0.2 - 0.07)[a]
2) TF vs M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.008 (0.004 - 0.75)[a]
4) HP - 0.08 (0.04 - 0.20)[a]

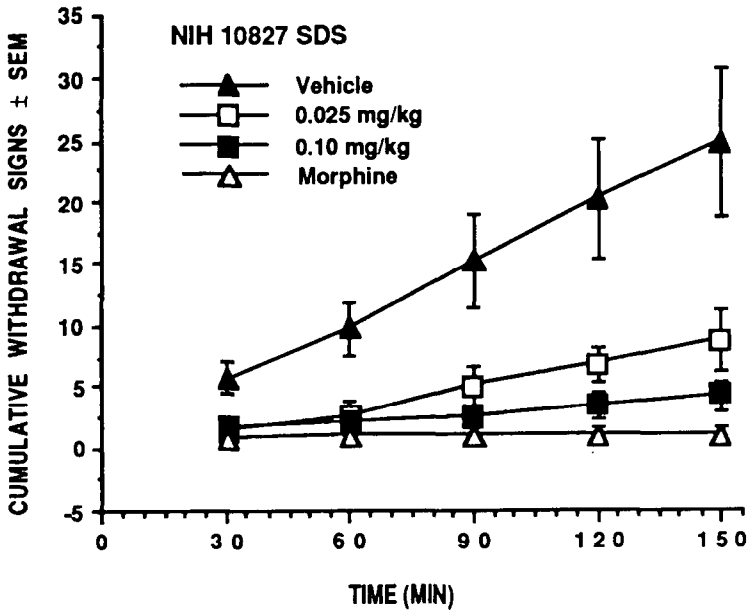
[a]Vehicle - lactic acid (1 gutta) in water

Special: Naloxone vs ED_{80} of NIH 10827 in TF - AD_{50} = 0.04 (0.02 - 0.11)

NIH 10827 (continued)

Monkey Data
SDS

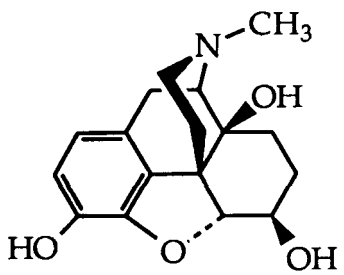
NIH 10827 substituted for morphine in maximally dependent rhesus monkeys at doses of 0.025 and 0.1 mg/kg. Onset was prompt as was offset. This substance is approximately 60 x more potent than morphine. Vehicle was dilute HCl and sterile water.



Comment:

NIH 10827 displays all the properties associated with a typical mu agonist.

NIH 10828 3,6β,14-Trihydroxy-17-methyl-4,5α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 1.37 (0.69 - 2.72)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.36 (0.16 - 0.87)[a]
4) HP - 2.73 (1.03 - 7.28)[a]

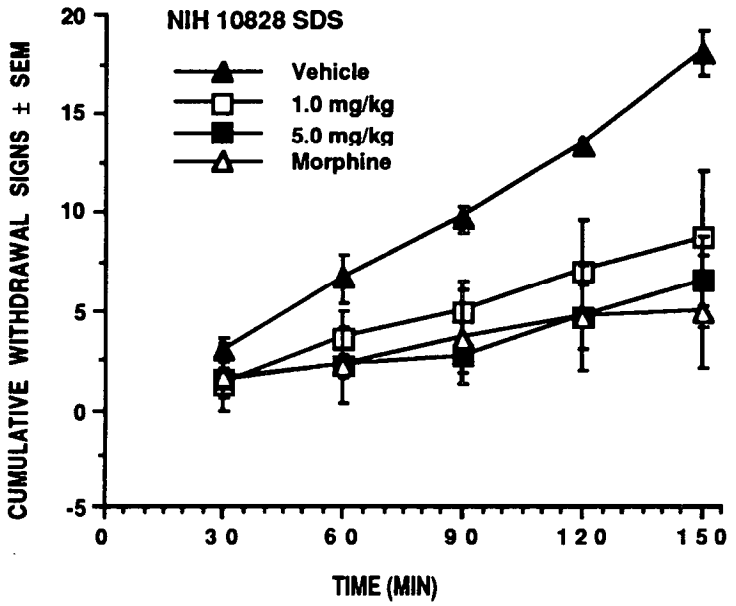
[a]Vehicle - 2 drops dil HCl in water

NIH 10828 (continued)

MONKEY

(SDS)

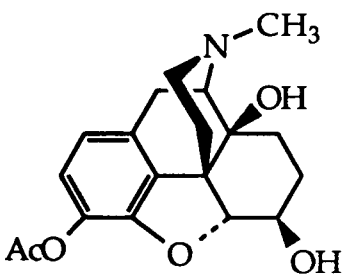
This substance attenuated withdrawal signs in abruptly withdrawn monkeys (see fig.). Onset and offset of actions similar to those of morphine. Approximately equipotent with morphine.



Comment:

The data suggest a mu agonist profile of activity for NIH 10828.

NIH 10829 3-Acetoxy-6β, 14-dihydroxy-17-methyl-4,5α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

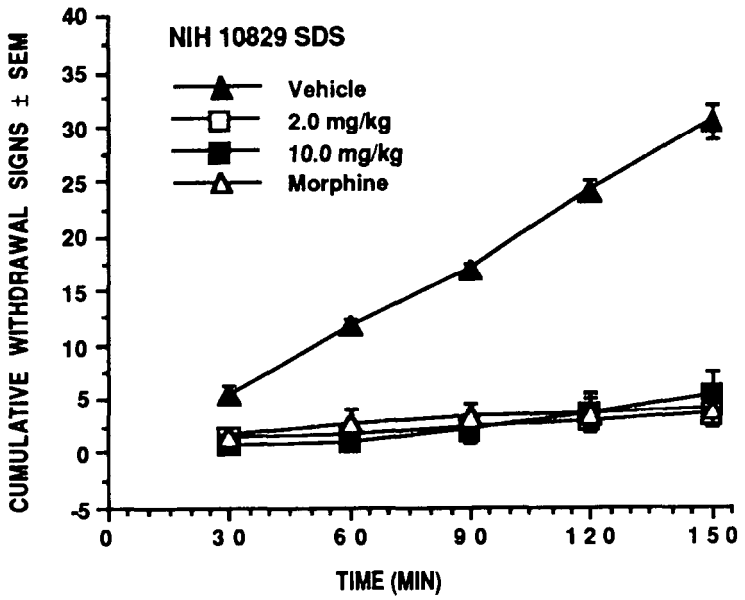
1) TF - 2.49 (0.94 - 6.58)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.24 (0.09 - 0.81)[a]
4) HP - 3.83 (2.09 - 7.06)[b]

[a]Vehicle - 5% hydroxypropylβ-cyclodextrin aqueous solution
[b]Vehicle - 1 drop lactic acid in water

NIH 10829 (continued)

MONKEY DATA
(SDS)

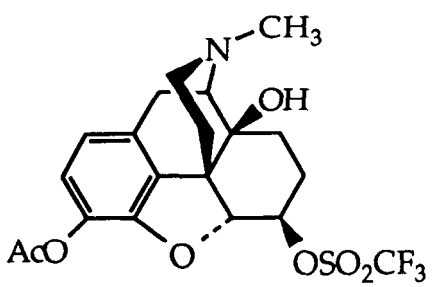
At 2.0 and 10.0 mg/kg, NIH 10829 substituted completely for morphine in withdrawn dependent monkeys (see fig.). Onset and duration of action were similar to morphine's. Approximately equipotent when compared with morphine•sulfate. Vehicle - 10% aqueous solution of hydroxypropyl-β-cyclodextrin.



Comment:

This compound has pharmacological properties similar to those of morphine.

NIH 10830 3-Acetoxy-6β-trifluoromethanesulyloxy-14-hydroxy-17-methy14,5 α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 0.09 (0.03 - 0.21)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.04 (0.02 - 0.08)[a]
4) HP - 0.22 (0.07 - 0.69)

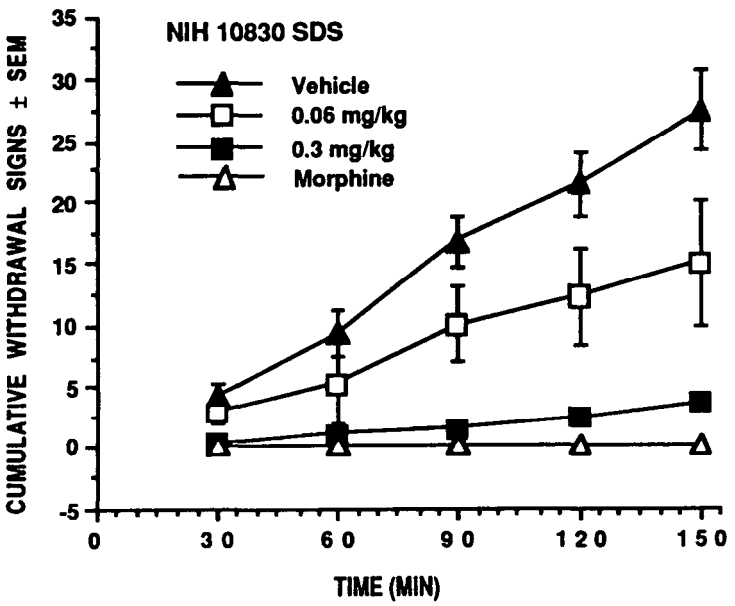
[a]Lactic acid in water

NIH 10830 (continued)

MONKEY DATA

(SDS)

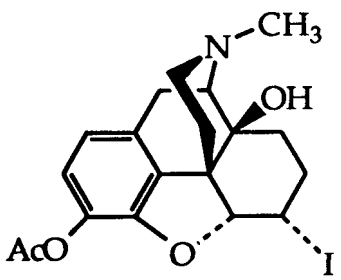
NIH 10830 dose-dependently substituted completely for morphine in the dose range of 0.06 to 0.3 mg/kg (see fig.). Onset is rapid and offset is less than that of the control morphine sulfate. Potency estimate is 10 x that of morphine. Vehicle was 10% hydroxypropyl-β--cyclodextrin plus 1 drop of dil HCl.



Conclusion:

This profile of activity is typical of mu agonists.

NIH 10831 3-Acetoxy-14-hydroxy-6 α--iodo-17-methyl-4,5α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 0.02 (0.01 - 0.05)[a]
2) TP vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.009 (0.004 - 0.02)[a]
4) HP - 0.06 (0.04 - 0.1)[a]

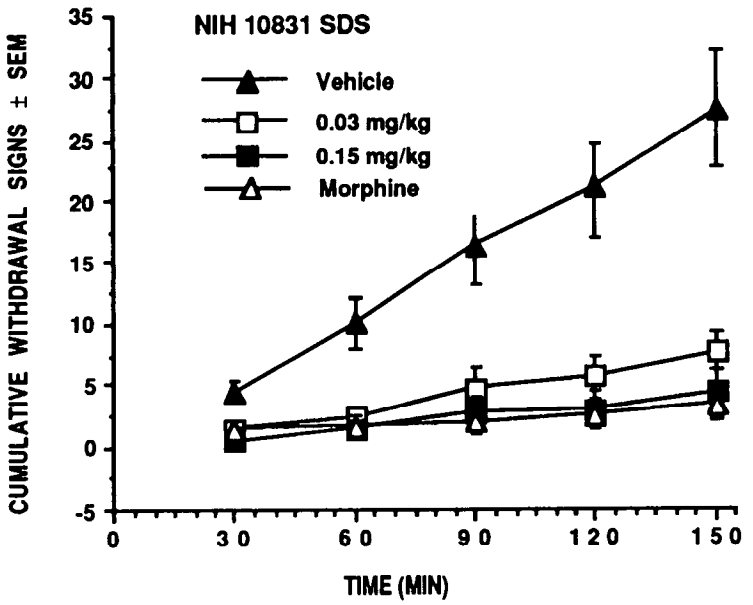
[a]Vehicle - Lactic acid (1 gutta) and water

NIH 10831 (continued)

Special: Naloxone vs ED_{80} of 10831 in TF - AD50 0.2 (0.1 - 0.4)

MONKEY
(SDS)

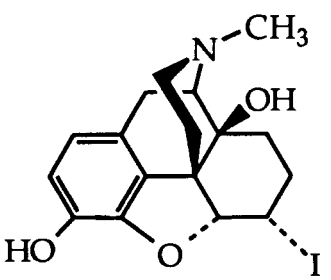
Over a half-log dose range (0.03 - 0.15), NIH 10831 attenuated withdrawal signs in abruptly withdrawn morphine-dependent monkeys. Onset was rapid and duration of action was shorter than morphine's. Potency estimate is approximately 75 x that of morphine sulfate. Vehicle was 10% hydroxypropyl-β-cyclodextrin in sterile water.



Bottom Line:

Except regarding potency, NIH 10831 is remarkably like morphine•SO_4 in its actions. The high AD50 with naloxone also suggests kappa activity.

NIH 10832 14-Dihydroxy-6α-iodo-17-methyl-4,5 α-epoxymorphinan



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

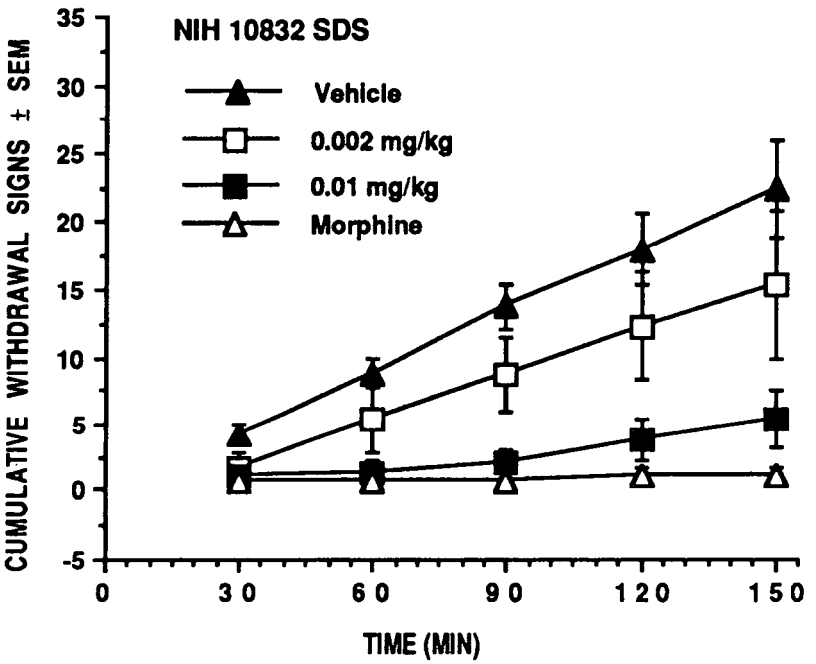
1) TF - 0.02 (0.01 - 0.04)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
3) PPQ - 0.1 (0.005 - 0.02)[a]
4) HP - 0.02 (0.007 - 0.04)[a]

[a]Vehicle - 3 drops dil HCl in H_2O

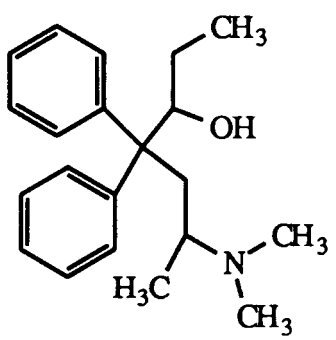
NIH 10832 (continued)

MONKEY DATA
(SDS)

As shown in the figure, NH 10832 dose-dependently attenuated withdrawal at 0.02 and 0.01 mg/kg. Onset was prompt and similar to that of morphine. Potency estimate is 300 x morphine. Vehicle was dilute HCl.



NIH 10837 (NIH 4552) α-(-)-6-Dimethylamino-4,4-diphenyl-3-heptanol•HCI (α-Levomethadol, α-1-methadol)



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

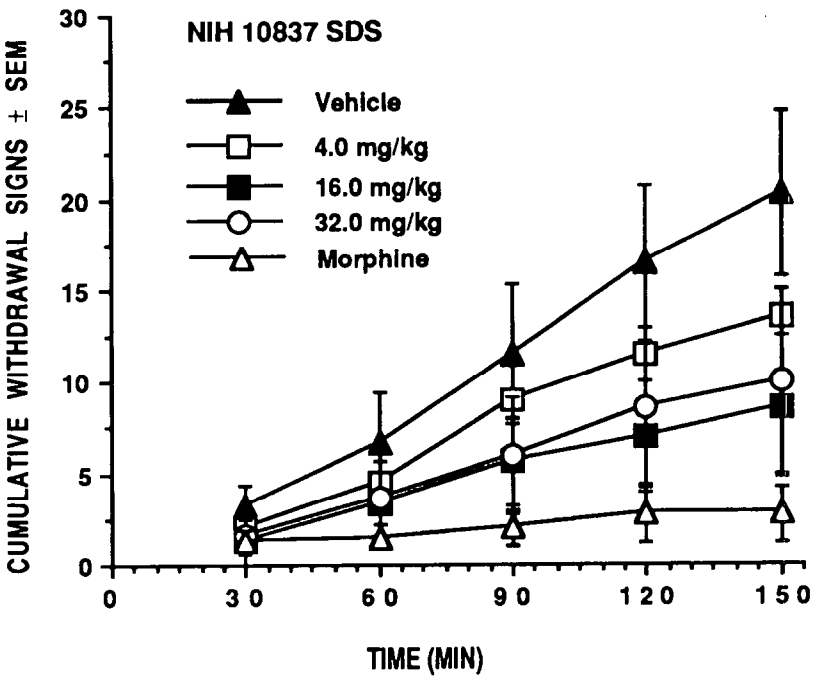
1) TF - 13.9 (10.2 - 18.8)
2) TF vs M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 1.9 (1.0 - 3.6)
4) HP - 4.9 (2.9 - 8.2)

NIH 10837 (NIH 4552) (continued)

MONKEY DATA
(SDS)

Study 1 - Questionable results with n=2. Supply exhausted. Reported 9/12/94.

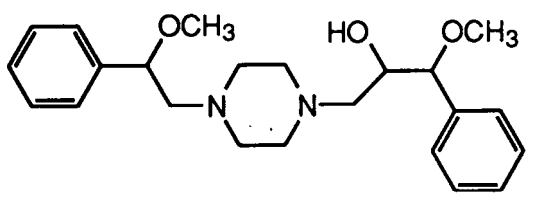
Study 2 - As shown in the fig., NIH 10837 attenuated withdrawal but did not substitute completely for morphine. The two higher doses produced essentially the same degree of suppression. Retching, vomiting and wet-dog shakes were the withdrawal signs least affected. Onset of action was prompt and offset was about an h.



Comment:

The data suggest that NIH 10837 has weak mu agonist activity.

NIH 10843 Zipeprol [4-(2-Methoxy-2-phenylethyl)-α-(methoxyphenylmethyl)-1-piperazineethanol •2HCl]



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 17% at 1.0, 28% at 10.0, 43% at 30.0[a]
2) TF vs M - Inactive at 1.0, 10.0 or 30.0
3) PPQ - 8.72 (3.61-21.07) Slope 2.93
4) HP - 13% at 1.0, 13% at 10.0, 25% at 30.0

[a]Decreased locomotion at 30.0 mg/kg
[b]Some ataxia and eyelid ptosis at 25.0 mg/kg
Decreased locomotor activity and eyelid ptosis at 20.0 mg/kg

NIH 10843 (continued)

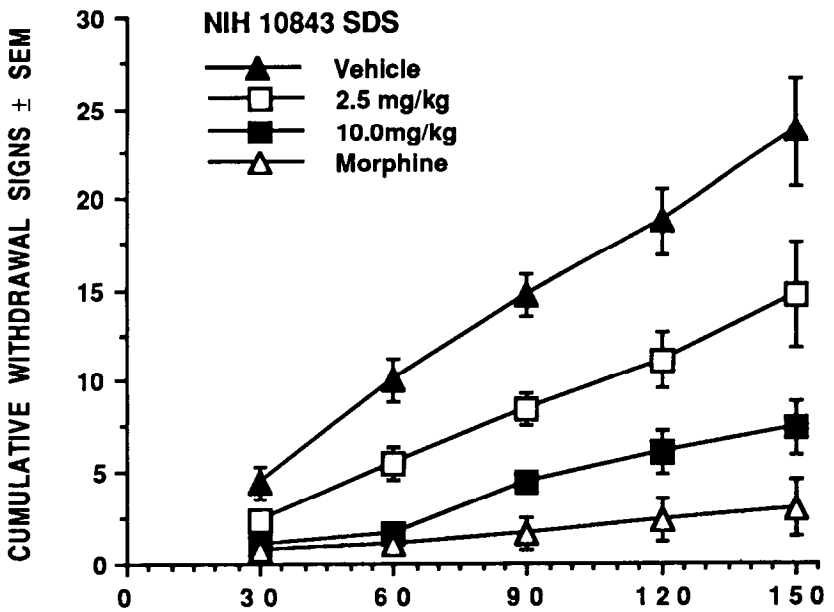
Special: Naloxone vs ED_{80} of 10843[b] in PPQ Test

29% antagonism at 1.0 mg/kg naloxone
55% antagonism at 10.0 mg/kg naloxone
58% antagonism at 20.0 mg/kg naloxone

MONKEY DATA

(SDS)

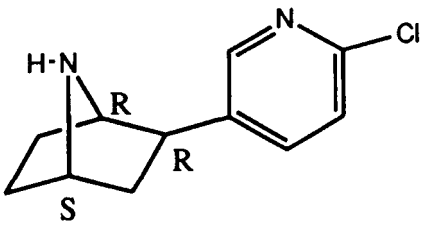
As can be seen in the depicted data, NIH 10843 dose-dependently suppressed withdrawal in morphine-dependent monkeys. Onset of action was rapid; however, duration was approximately 90 m. The drug is 1/4 as potent as morphine at peak effect. At the high dose, scratching, ataxia, sagging and slowing were observed. These signs are usually seen in non-tolerant monkeys receiving morphine or in tolerant monkeys receiving 3-4 times the dose of morphine required to suppress withdrawal.



Comments:

There appears to be a dissociation between the mouse and monkey data. In the monkey, NIH 10843 has mu agonist properties, whereas it appears devoid of opioid properties in the mouse.

NIH 10850 1*R*,2*R*,4*S*-(+)-Epibatidine hemioxalate (from natural (-)-epibatidine base)



MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF - 12.5 (8.8-17.6)[a] µg/kg
2) TF vs M -
3) PPQ - 1.6 (0.7 - 3.3)[a] µg/kg
4) HP-

[a]5 m pretreatment time
note, dose is ug/kg

Special Tests

1) Naloxone vs ED80 of (+)-epibatidine in TF = 19% antagonism at 0.1, 38% antagonism at 1.0, 51% antagonism at 10.0, 2% antagonism at 20.0.

2) Naloxone vs ED50 of (+)-epibatidine in PPQ. Inactive at 0.1, 1.0 and 10.0

3) Mecamylamine/(+)-epibatidine pA_2 in PPQ: pA_2 = 6.2 (6.2-6.2) slope = 0.98

NIH 10851 1*S*,2*S*4*R*-(-)-Epibatidine hemioxalate (from unnatural (+)-epibatidine base)

MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

SEE NIH 10850

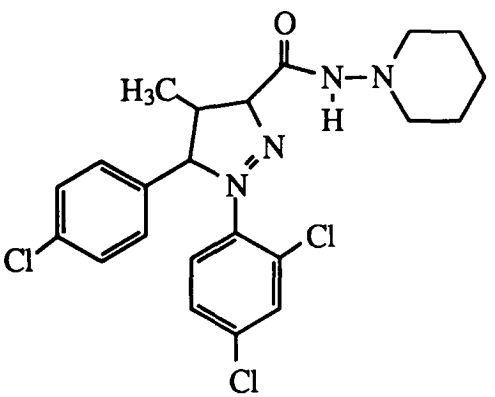
1) TF - 8.6 (6.3 - 11.9)[a] µg/kg
2) TFvsM -
3) PPQ - 0.8 (0.2 - 2.5)[a] µg/kg
4) HP-

[a]5 m pretreatment time

a) Naloxone AD50 vs ED80 of (-)-epibatidine in TF = 0.1 (0.03 - 0.72) mg/kg

b) Naloxone AD50 vs ED80 of (-)-epibatidine in PPQ = 0.02 (0.004 - 0.09) mg/kg

NIH 10859 SR141716A [N-(-piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H pyrazole-3-carboxamide•HCl



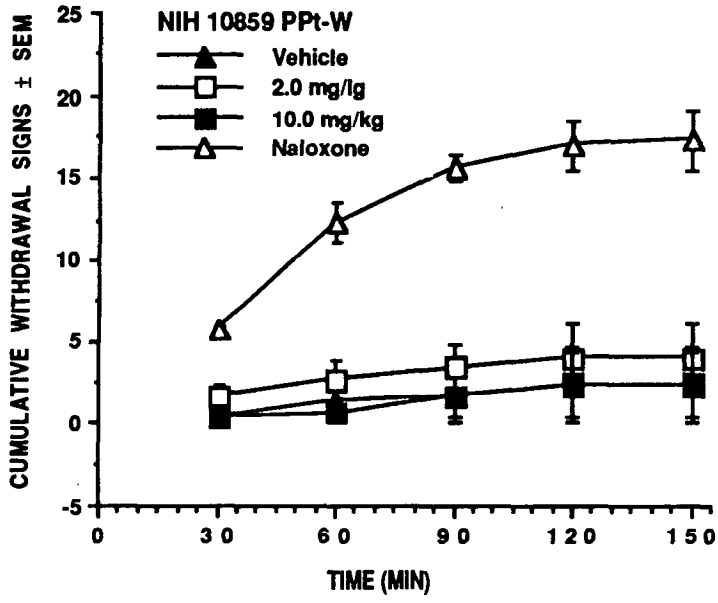
MOUSE DATA-ED50 or AD50
(95% C.L.) or % change (mg/kg)

1) TF-NT
2) TF vs. M - NT
3) PPQ-NT
4) HP-NT

NIH 10859 (continued)

MONKEY DATA
(PPt-W)

SR141716A precipitated withdrawal in Δ^{9}-tetrahydracannabinol (THC)-infused rats (see NIH 9051). In order to determine the selectivity of this antagonist, and determine whether or not it interacted with opioids. this study was conducted. As depicted in the figure, SR141716A did not precipitate withdrawal in morphine-dependent monkeys at doses of 2 and 10 mg/kg. It also produced no overt behavioral effects of its own at these doses. Vehicle was 20% dimethyl sulfoxide in propylene glycol.



Conclusion:

SR141716 appears selective in its interaction with Δ^{9}-THC.

ACKNOWLEDGEMENTS

This study was supported by a contract (#271-90-7200 and 3-8200) from the National Institute on Drug Abuse. We also acknowledge the expert assistance of Susan M. Tucker, and Larry Hughes, and Zhen Ji. Special thanks to Laura Johnson for her help in the preparation of this manuscript using the Macintosh IIci.

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PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUGS (1995)

J. A. English; J. K. Rowlett; W. L. Woolverton; G. A. Patrick; W. T. Hawkins; G. Winger and J. H. Woods

University of Mississippi Medical Center, Jackson, MS; Medical College of Virginia/Virginia Commonwealth University, Richmond, VA; University of Michigan, Ann Arbor, MI

The research group involved in the evaluation of stimulant and depressant compounds has been in existence for approximately 12 years. The group includes laboratories at Virginia Commonwealth University (Patrick, Hawkins), the University of Mississippi Medical Center (Woolverton, Rowlett, English), and the University of Michigan (Winger, Woods). The group is part of the Drug Evaluation Committee, chaired by Ted Cicero, of the College on Problems of Drug Dependence (CPDD) and is supported by both CPDD and NIDA. One of the purposes of the group is to evaluate new compounds, generally classified as either stimulants or depressants, for their abuse liability and potential to produce dependence. Compounds are received, coded and distributed by Dr. Arthur Jacobson at NIH for blind testing in the various laboratories. They are evaluated for discriminative stimulus effects (UMMC), reinforcing effects (UM), and capacity to produce physical dependence and potency in production of central depressant effects (VCU). This report includes the results of evaluation of the following compounds: CPDD-0042 and CPDD-0043.

METHODS

Reinforcing Effects in Rhesus Monkeys

Subjects

Subjects were rhesus monkeys (Macaca mulatta) experienced with self-administration of sodium methohexital and saline. Animals were surgically prepared with indwelling silicone rubber catheters using 10 mg/kg i.m. ketamine and 2.0 mg/kg i.m. xylazine as anesthetics. Catheters were implanted in jugular (internal or external), femoral or brachial veins as necessary. Catheters passed subcutaneously to the mid-scapular region, exited the body and continued, through a hollow restraining arm, to the outside rear of the cage.

Apparatus

The restraint and catheter protection device and described in detail by Deneau *et al.* (1969). Each monkey wore a tubu1ar stainless steel harness that protected the exit site of the catheter and allowed relatively unresricted movements within the cage. A Tenon cloth jacket (Alice King Chatham Medical Arts, Los Angeles, CA) provided further protection for animals who tended to locate and pull their catheters. The harness was connected to a flexible spring arm that carried the catheter to the back of the cage where it joined tubing passing through a roller infusion pump (Watson and Marlow Co., Model MHRK 55, Falmouth, UK).

Monkeys were individually housed in stainless steel cages, measuring 83.3 X 76.2 X 91.4 cm deep. A 15.4 cm square stimulus panel was located on the side of each cage, approximately 10 cm from the front and 19 cm from the bottom of the cage. Across the top of the stimulus panel, 2.5 cm apart. were three circles, 2.5 cm in diameter, covered with translucent plastic and capable of being illuminated from behind by 5 W colored bulbs. The two side lights could be illuminated red and the center light green. Below each of the two red stimulus lights was a response lever (Model 121-07; BRS-LVE, Beltsville, MD) capable of being operated by a force of 0.010 to 0.015 N. Experimental control was provided by an IBM PS/2 computer programmed with Med-PC (Med-Associates, Fairfield, VT) software and located in an adjoining room.

Procedure

Reinforcing effects were evaluated in a substitution self-administration procedure with methohexital serving as the baseline drug. Test sessions and baseline sessions had the same general structure: At the start of each session, a red light was illuminated over one of two levers in each monkey's cage. When an animal completed the fixed-ratio

requirement of 10 presses on that lever (fixed-ratio 10; FR10) a S-second, 1 .0 ml injection of saline solution, sodium methohexital (0.1 mg/kg), or a test compound, was delivered. During an injection, the red lever light was extinguished and the center green light illuminated for the duration of the infusion. Each injection was followed by a 10-second time-out during which all stimulus lights were extinguished and responding had no programmed consequence.

Experimental sessions lasted 130 min. Two sessions were scheduled each day. On approximately half of the baseline sessions, the monkeys were exposed to response-contingent saline. All animals showed clear and consistent differential responses to saline and methohexital before test compounds were substituted.

In test sessions a dose of the test compound was made available for one session. Other conditions were similar lo those of the baseline sessions. Each dose of each test compound was tested at least twice in each animal.

Drugs

All drugs were given in an injection volume of 1.0 ml. CPDD-0042 and 0043 were dissolved in saline solution. The methohexital training close was 0.1 mg/kg/injection. CPDD-0042 doses were 0.001, 0.003, 0.01, 0.03, and 0.1 mg/kg/injection. CPDD-0043 doses were 0.001, 0.003, 0.01, and 0.03 mg/kg/injection.

Discriminative Stimulus Effects in Rhesus Monkeys

Subjects

The subjects were one female and six male rhesus monkeys (Macaca mulatta) weighing between 6.4 and 10.6 kg. Monkeys were housed individually in stainless steel cages in which water was continuously available. They were fed 150 to 200 g of Teklad monkey chow after each session and were given a chewable vitamin tablet 3 days/week.

The monkeys had been trained previously to discriminate d-amphetamine (AMPH: 7739, 8405, 8515) or pentobarbital (PB: Ef3, 8236, 8814, 8902) from saline in a two-lever, discrete-trial shock avoidance procedure. All monkeys except Ef3 had received other test drugs prior to testing CPDD-0042 and CPDD-0043.

Apparatus

During experimental sessions animals were seated in primate restraint chairs and placed inside sound-attenuating cubicles. All chairs were fitted with shoes that had brass plates in the soles that permitted delivery of electric shocks with a shock generator (5% 903 BRS/LVE, Laurel, MD). Chambers were equipped with two response levers (PRL-001, BRS/LVE, Laurel MD) mounted on one wall. There were four white lights above each lever. Chambers well: illuminated with ceiling-mounted 40W incandescent house lights mounted on the ceilings. Experimental events were programmed and recorded with an Apple Macintosh II computer in a room adjacent to the one in which animals were tested.

Procedure

The training and test procedures have previously been reported in detail (Woolverton et al., 1994). A monkey was placed in the restraint chair and either saline (1-2 ml) or the training drug was administered, intragastrically via a nasogaslric tube, followed by a 1.5 ml saline flush. The monkey then was returned to its home cage. Fifty-five minutes after infusion, the monkey was placed again in the restraint chair and then into the experimental chamber.

The session began with a 5-min timeout. There were 30 trials. On each trial the houselight and lever lights were illuminated and responding on the correct lever avoided electric shock and extinguished the lights. Responding on the incorrect lever reset the response requirement on the correct lever. The correct lever was determined by the pre-session infusion (drug or saline). If the response requirement (FR 1, 2 or FR 5) was not met on the correct lever within 5 sec (10 set for FR 5) of the onset of the lights, shock (250 msec duration, 3 or 7 mA intensity) was delivered. If the response requirement was not met within 2 sec (4 sec for FR 5) of this shock, a second shock was delivered and the trial automatically ended. Two consecutive trials in which 2 shocks were received automatically ended the session. Trials were separated by 30-sec timeouts.

Training sessions were conducted five days a week according to the following schedule: SDDSS, DSSDD, where S denotes sessions preceded by saline and D denotes sessions preceded by drug. Discrimination training continued until at least 90% of the responses in the first trial were on the correct lever and at least 90% of the total trials (27/30) were avoidance trials for seven out of eight consecutive sessions. When performance met these criteria the sequence SDTST DSTDT was used, with S and D as above and T denoting test sessions. If an animal's performance drifted off criterion the training sequence was run until performance was again at criterion.

Test sessions were like training sessions except that test drugs were used and completing the response requirement on either lever avoided shock.

Drugs

A stock solution of d-amphet;unine sulfate (AMPH; National Institute on Drug Abuse, Rockville, MD) was dissolved in saline in a concentration of 5.0 mg/ml. The training dose of AMPH was 0.56 mg/kg for animals 8405 and 7739; it was 1.0 mg/kg for animal 8505. PB was mixed daily by diluting Nembutal (Abbott Laboratories, N. Chicago, IL). The training dose was 10 mg/kg for all PB-trained animals. CPDD 0042 doses were 0.3, 1.0, 3.0, and 10.0 mg/kg (one monkey). CPDD 0043 doses were 0.1, 0.3, 1.0, 1.7, 3.0, and 10.0 mg/kg. All drugs were prepared in saline. The infusion volume was 0.25 ml/kg.

Physical Dependence Studies in Rats

Subjects

Male Sprague-Dawley rats (Harlan Laboratories), weighing 175 to 225 g at the start of the experiments, were used in the chronic infusion and substitution experiments. They were individually housed in the Departmental animal facility and maintained in an alternating 12-hour light-dark environment (light 0730 to 1930 hours). The infusion experiments were performed in a designated room within the animal facility. Four to six rats were included in each treatment group.

Apparatus

Chronically placed intraperitoneal cannulae were used for drug infusions. Harnesses limited animals' access to the cannulae. Drugs were administered with Harvard infusion pumps connected to 10-ml syringes that in turn connected to cannulae via flow-through swivels.

Procedure

Rats were surgically prepared with intraperitoned cannulae as described by Teiger (1974). Rats were anesthetized with methoxyflurane (Pitman-Moore Inc.), the abdomen was incised, and a PE-50 cannula was inserted into the peritoneal space and was sutured to the abdominal muscle at the point of exit to secure it. The free end of the cannula was advanced subcutaneously to exit the body through a small incision at the nape of the neck, where it was also sutured in place. All procedures were performed using aseptic technique. All cannulae and surgical instruments were placed in antiseptic solution before use. Rats were allowed at least two days of recovery before initiation of the study.

Upon recovery from surgery, rats were secured in harnesses to reduce access to the cannulae and were placed in individual cages. Before administration of drugs, all rats were acclimated to the infusion apparatus for at least two days, during which they received saline infusions. Control rats continued on saline infusion throughout the course of experimentation. Drug-treated rats were infused with a solution of either sodium pentobarbital made isotonic with sodium chloride or with cocaine hydrochloride in physiological saline. Drug solutions were drawn into syringes and diluted with physiological saline so that the desired dosage was administered in a volume of 8 ml/24 hours (4 ml/24 hr during weekends). Drugs were administered by continuous infusion on an escalating dosage schedule for 12 days. Dosage of pentobarbital (expressed as the free acid) was initiated at 100 mg/kg-day, and was increased at a rate of 0 to 100 mg/kg-day depending on the degree of depression of the animal. By day 12, most rats were receiving pentobarbital at a rate of 900 to 1000 mg/kg-day. Body weights of rats were measured daily during the period of infusion.

After 12 days of infusion of pentoharbital, infusion lines were disconnected from the internal cannulae and flushed with saline. Each rat was then infused for 24 hours with a solution of the test compound (CPDD-0042 or CPDD-0043) or with saline (vehicle) -- the substitution phase. Following substitution of drug, infusion lines were flushed with saline again, and all rats were infused for 24 hours with saline solution -- the withdrawal phase.

During the substitution and withdrawal phases of the experiment, a number of observations were made to assess signs of withdrawaI in the rats, For all rats, body weight was determined at 8 and 24 hours of each day. In pentobarbital-infused rats, overt behavioral signs of hyperexcitability were assessed every 2 hours for the first 8 hours of day the substitution day and every four hours for the first 8 hours of the withdrawal day, and at 24 hours of each day. At each of those time points, each rat was assigned a withdrawal score based on the following seven-point rating scale:

a) Response to puff of air directed at head: 0 - no response; 1 - jumps (does not include flinch); 2 - jumps and vocalizes.

b) Squeal when prodded with a blunt instrument: 0 - no response; 1 - vocalizes.

c) “High” or “aggressive” posture (standing with all 4 legs extended, back arched, with or without piloerection): 0 - no high posture; 1 - high posture.

d) Response to being grasped and held gently but firmly for a few seconds: 0 - no response; 1 - struggles or vocalizes; 2 - struggles and vocalizes; 3 - struggles, vocalizes, and claws and/or bites.

The raters scoring rats were blind as to the treatment received by each rat.

Drugs

CPDD-0042 was dissolved in distilled water. The drug solution or vehicle (in control animals) was given by i.p. infusion in a volume of 8 ml/clay.

CPDD-0043 was dissolved in isotonic saline solution. It was given via i.p. infusion in a volume of 8 ml/day.

Analyses

The withdrawal scores for each treatment group were analyzed for significant variation from other groups of interest using the Mann-Whitney U test. The data relating to changes in body weight and to food and waler consumption were tested for significance by analysis of variance and paired t-test.

Potency Estimation in Mice

Subjects

Male CD-1 albino mice (Harlan Laboratories, Dublin, Virginia), weighing 25 to 40 g, were used in the study of locomotor activity and in the inverted screen test. Mice were housed 5 per cage in the Departmental animal facility and maintained in and alternating 12-hour light-dark environment (light 0730 to 1930 hours). Food and water were available ad libitum. Four to eight mice were used per treatment group.

Apparatus

Locomotor activity (gross walking movements) of the mice was measured in a cage in which movement in inside the cage interrupts beams of infrared light which traverse the cage. The interruption of three consecutive beams, spaced 1 inch apart, was detected by a sensor and recorded as a “count” of activity (Omnitech, Columbus, Ohio).

The inverted screen test was conducted using a 12.8 cm x 12.8 cm screen with a 6 mm mesh.

Procedure

Locomotor Activity

Experiments were performed between 0900 and 1500 hours in a laboratory separate from the animal facility. One mouse was placed in each cage, enclosed in a cabinet to exclude external stimuli, and locomotor activity was monitored. The effect of each dose of the drug was calculated and expressed as the percentage of locomotor activity recorded for concomitantly tested mice given vehicle. Measurement of locomotor activity was made during the following time intervals after the drug (or vehicle control) administration: 5 to 15 min, 35 to 50 min, 65 to 95 min, and 125 to 185 min.

Inverted Screen Test for Muscular Function

Each mouse was placed on a wire screen (12.8 cm x 12.8 cm with a 6 mm mesh) and the screen was then inverted. A positive effect of the drug is to cause the mouse to fall from the screen within 60 seconds. A negative effect is the ability of the mouse to climb from the underside of the screen to the top side of the screen within the 60 second time period. Hanging from the underside of the screen at 60 seconds is recorded as a one-half positive effect (Coughenour et al., 1977). The test was performed at 30, 60, 120 and 240 minutes following administration of drug or vehicle.

Drugs

CPDD-0042 was dissolved in isotonic saline solution for the acute experiments in mice and in distilled water for the infusion in rats. The drug solution or vehicle (in control animals) was given by i.p. injection to mice in a volume of 10 ml/kg or by i.p. infusion to rats in a volume of 8 ml/day.

CPDD-0043 was dissolved in isotonic saline solution. In mice, the drug solution or vehicle (in control animals) was given by i.p. injection in a volume of 10 ml/kg. It was given to rats via i.p. infusion in a volume of 8 ml/day.

Analysis

In locomotor activity studies, the mean number of counts of activity (+ S.E.M.) was determined for each experimental group. A two-tailed t-test was used to determine significant differences between each test group and its control group. Data from the inverted screen test did not permit ED-50 calculation for CPDD-0042.

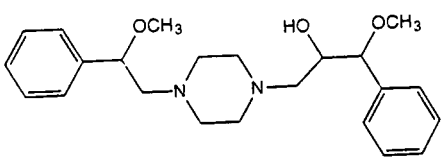
RESULTS

CPDD-0042

Reinforcing Effects in Rhesus Monkeys

Five doses of CPDD-0042 were evaluated in the three monkeys. Each of the monkeys was tested at least twice with each dose. Figure 1 shows the effects of increasing dose of CPDD-0042 on self-administration. When CPDD-0042 was available, the number of injections was above saline levels at one or more doses in all three animals tested. There was a biphasic dose-effect relationship in all animals, with the greatest number of drug injections occurring at a dose of 0.03 mg/kg/injection in all cases. The maximum number of CPDD-0042 injections was comparable to the number of injections of methohexital (0.1 mg/kg/injection) in two animals, and substantially higher than the number of methohexital injections in the third animal.

Zipeprol [4-(2-Methoxy-2-phenylethyl)- α -(methoxyphenylmethyl)-1-piperazineethanol.2HCl]



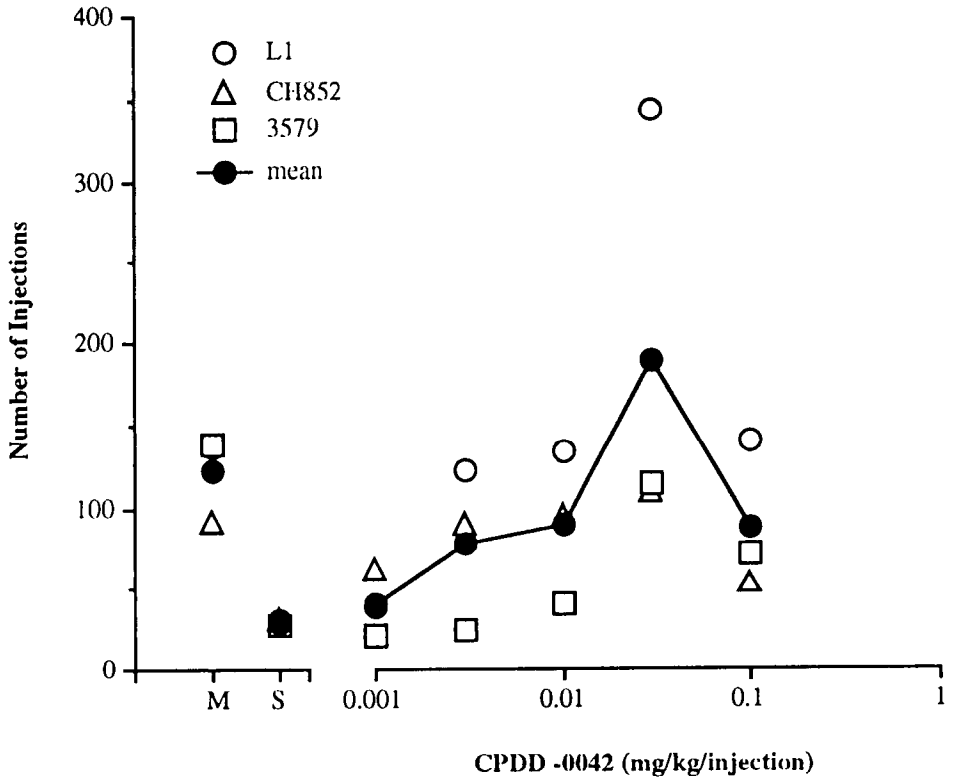


Figure 1. Self-Administration of CPDD-0042 by rhesus monkeys.

Discriminative Stimulus Effects in Rhesus Monkeys

CPDD 0042 engendered no drug-appropriate responding in either AMPH- or PB-trained monkeys (Tables 1 and 2). Response rate was not systematically affected by CPDD 0042. Monkey 8236 died within 30 minutes of receiving 10 mg/kg CPDD 0042.

Table 1
Discriminative stimulus effects of intragastric administration
of CPDD 0042 in AMPH-trained monkeys

			CPDD 0042 (mg/kg)			
Subject	AMPH	Saline	0.3	1.0	3.0	10.0
7739	100/0.93	0/1.03	0/0.9	0/0.93	0/1.43	nt
8515	100/3.02	0/2.14	0/2.40	0/3.0	0/2.61	nt
8405	100/1.16	3/1.36	0/1 .75	0/1.13	0/1.19	nt

Data represent the percent drug-appropriate trials/average latency per trial for 7739 and percent drug-appropriate trials/average response rate per trial (resp/sec) for 8515 and 8405. The training dose was 0.56 (7739,8405) or 1.0 mg/kg (i.g.) AMPH The response requirement was FR 1 for 7739 and FR 2 for 8515 and 8405. In all cases 30 trials were completed. nt=not tested.

Table 2
Discriminative stimulus effects of intragastric administration of CPDD 0042 in PB-trained monkeys

			CPDD 0042 (mg/kg)			
Subject	PB	Saline	0.3	1.0	3.0	10
Ef3	100/1.78	0/4.20	0/4.12	0/4.26	0/4.47	nt
8814	100/1.83	0/1.81	0/2.38	012.08	0/2.43	nt
8236	100/2.0	0/3.1	0/2.94	0/2.88	0/2.5	0/2.07

Data represent the percent drug-appropriate trials/average response rate (resp/sec). The training dose was 10 mg/kg (i.g.) for all animals. In all cases, 30 trials were completed. nt=not tested.

Physical Dependence Studies in Rats

When administered to rats undergoing withdrawal from pentobarbital, CPDD #0042 produced a slight, but not significant, reduction in overt behavioral signs of withdrawal (see Figure 2) The reduction only approached statistical significance from 24 to 32 hours following discontinuation of pentobarbital ($0.05<p < .10$) and was greater for the higher dose (500 mg/kg). Notably, that dose of #0042 infused into naive rats (Saline + CPDD-0042) did not cause depressant effects at all, but mild excitatory effects instead. Substitution of #0042 did not significantly alter the loss of body weight associated with barbiturate abstinence, as shown in figure 3. The pattern of weight loss was the same as in the saline-substituted rats, and was very nearly the same in magnitude. Interestingly, naive rats that received the higher dose of #0042 for 24 hours exhibited a slight increase in body weight relative to saline controls, but then showed some weight loss when the drug was withdrawn.

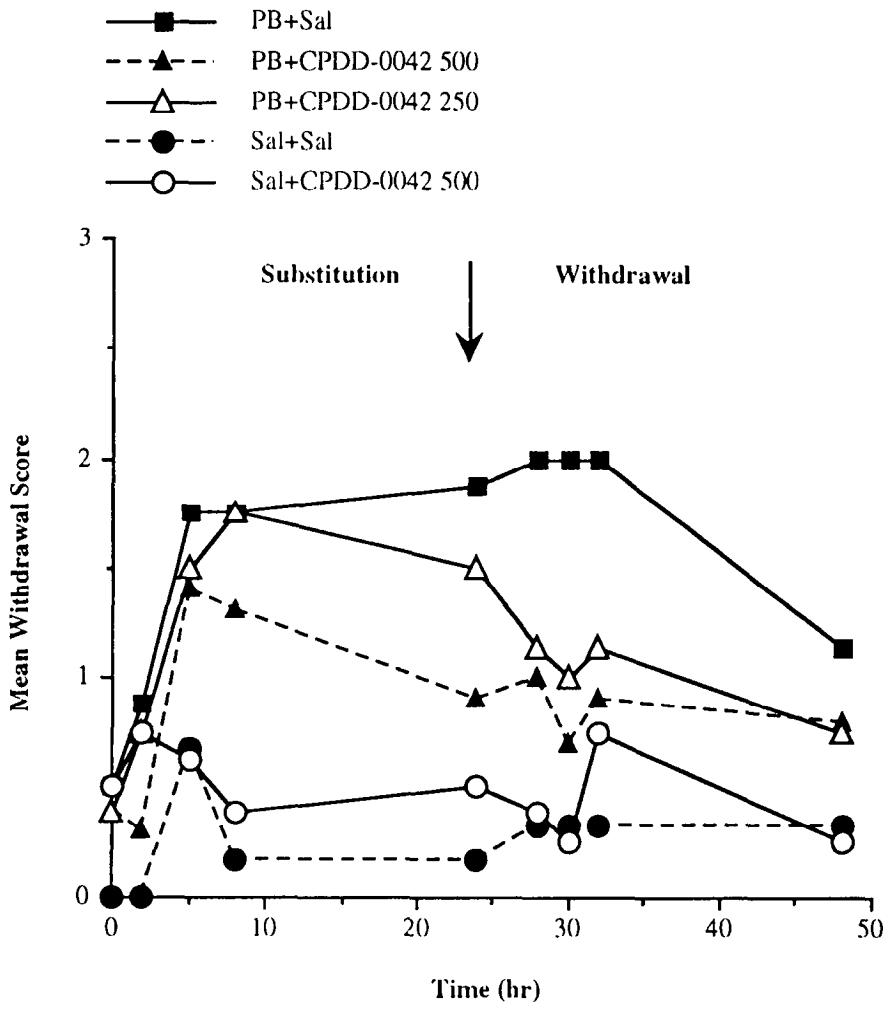


Figure 2. Withdrawal scores with substitution of CPDD-0042 or saline in pentobarbital-dependent rats

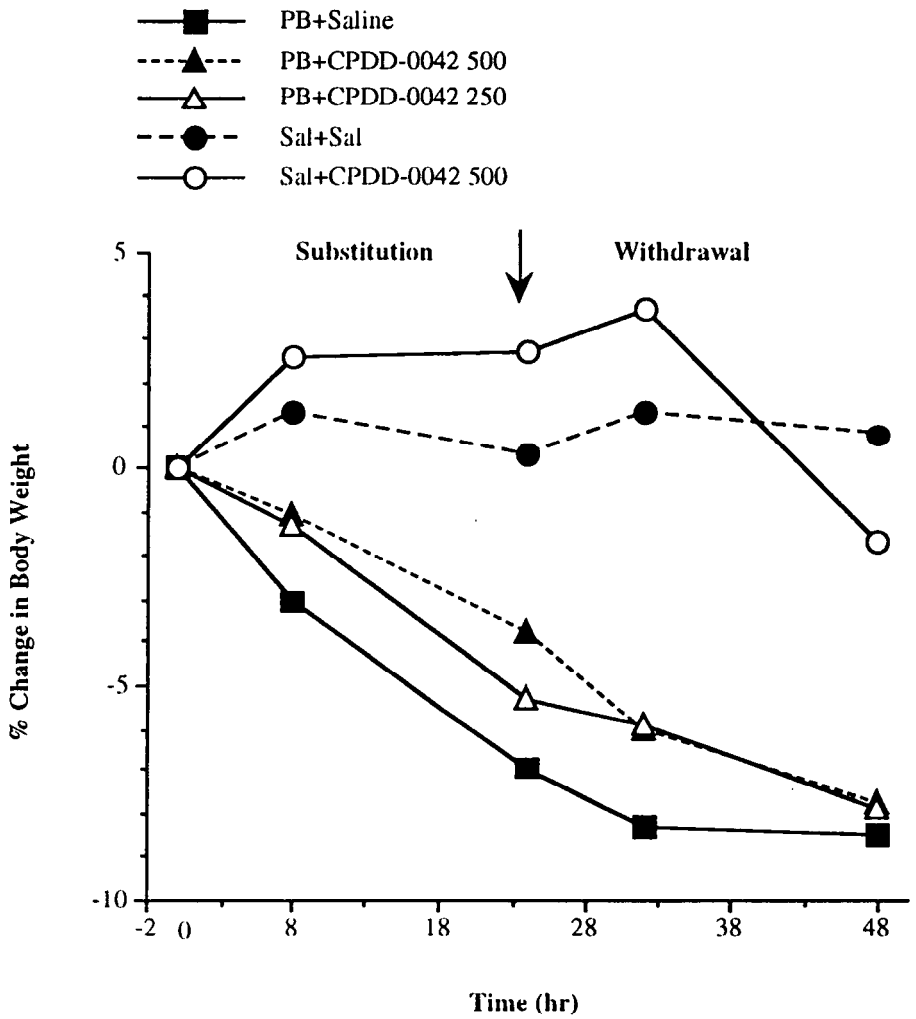


Figure 3. Changes in body weight with substitution of CPDD-0042 or saline in pentobarbital-dependent rats

Potency Estimation in Mice

Spontaneous Locomotor Activity

The effects of CPDD Compound #0042 on spontaneous locomotor activity are shown in Table 3 below.

Table 3: Effects of CPDD Compound #0042 on Spontaneous Locomotor Activity

Time after Treatment (min)

Dose (mg/kg)	5-15	35-50	65-95	125-185
0 (control)	55a	68.6	90	15.6
4	44	46.7	32.2	52
10	96	73.5	73.5	42.3
40	44.3	109	132	90.7

100		3.3	99	243
175	3.8	2	196	75.8
250	All 6 mice died within 15 min after treatment.			

a Values expressed as mean number of movements per mouse (N=6 for drug- treated groups; N=8 for control group.)

The effects of Compound #0042 on spontaneous locomotor activity were not consistently typical of either a stimulant or depressant drug. A mild stimulant effect appeared at the dose of 40 mg/kg, but it was neither profound nor clearly dose-related. At the higher doses (100 and 175 mg/kg) the mice exhibited profound depression which lasted for approximately 60 min and was followed by mild excitation. The 175 mg/kg dose caused some clonic movement with loss of righting for the first 30 min after treatment, apparently signs of toxicity although all mice recovered. The dose of 250 mg/kg caused similar signs in the brief period prior to death.

Inverted Screen Test

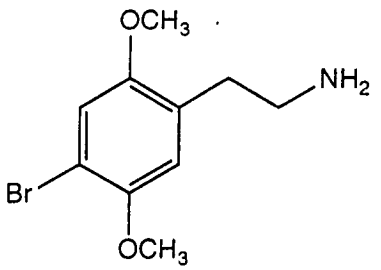
The lower doses of Compound #0042 (up to 10 mg/kg) produced no effects in the performance of this task The 40 mg/kg dose produced an effect of 25% impairment up to 30 min after treatment but INI effect at 60 min. Both the 100 and 175 mg/kg doses produced 100% failure rates at 30 min after treatment. For the 100 mg/kg dose the failure rate declined to 17% at 60 min and 0% at 120 min, while the 17.5 mg/kg dose caused 83% failure at 60 min and 25% failure at 120 min after injection.

CPDD-0043

Reinforcing Effects in Rhesus Monkeys

Four doses of CPDD-0043 were evaluated in the three monkeys. Each of the monkeys was tested at least twice with each dose. Figure 4 shows the numbers of injections of CPDD-0043 for three animals at four doses. The number of CPDD-0043 injections was above saline levels at two doses in one of the three animals tested (LI). For this animal the number of injections at doses of 0.003 and 0.01 mg/kg injections was comparable to the number of injections of methohexital (0.1 mg/kg/injcction). At higher (0.03 mg/kg/injection) and lower (0.001 mg/kg/injection) doses of CPDD-0043 the number of injections was comparable to the number of saline injections. For the other two animals the numbers of CPDD-0043 injections were similar to the numbers of saline injections.

4-Bromo-2,5-dimethoxy- b -phenethylamine hydrochloride



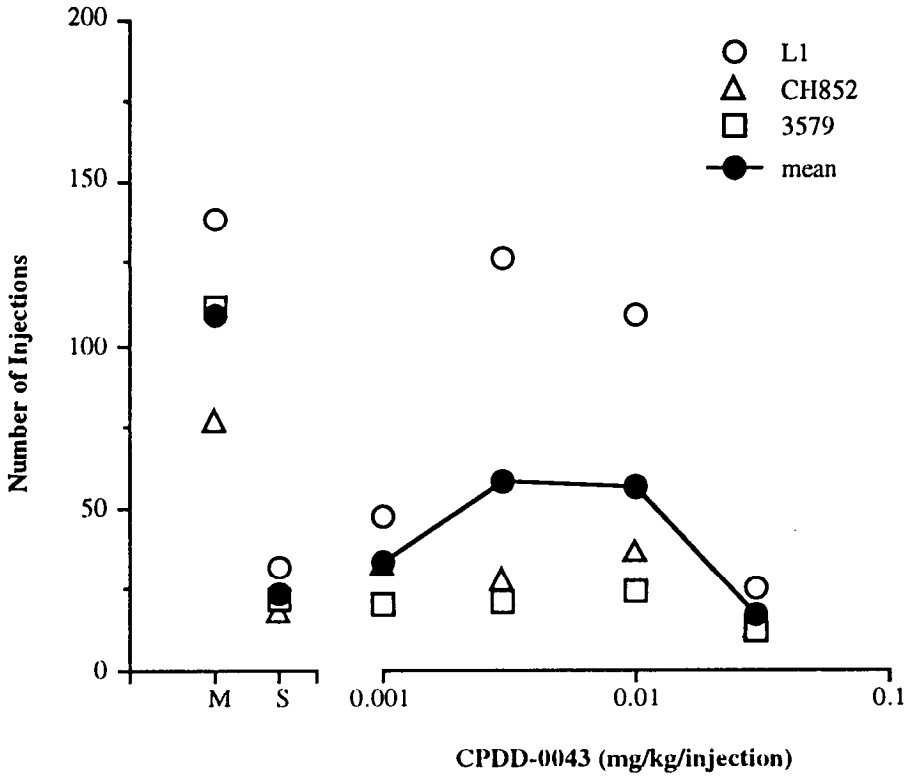


Figure 4. Self-administration of CPDD-0043 by rhesus monkeys.

Discriminative Stimulus Effects in Rhesus Monkeys

CPDD 0043 engendered no drug-appropriate responding in either AMPH- or PB-trained monkeys (Tables 4 and 5). Response rate was not systematically affected by CPDD 0043, although 3.0 mg/kg CPDD 0043 completely suppressed responding in one PB-trained monkey.

Table 4
discriminative stimulus effects of intragastic administration
of CPDD 0043 in AMPH-trained monkeys

		CPDD 0043 (mg/kg)				
Subject	AMPH	Saline	0.1	0.3	1.0	3.0
7739	100/1.63	3/1.22	nt	20/1.44	0/1.44	0/1.25
8515	100/2.34	0/2.5	0/0/1.23	0/1.33	0/2.00	0/3.0
8405	100/1.16	0/1.08	nt	nt	3/1.38	0/1.19

Data represent the percent drug-appropriate trials/average response rate per trial (resp/sec) for 8515 and 8405. The response requirement was FR 2 for 7739 and 8405, and FR 3 for 8515. CPDD 0043 was administered via nasogastric tube 60 minutes before testing. In all cases 30 trials were completed. nt=not tested.

Table 5
Discriminative stimulus effects of intrragastric administration
of CPDD 0043 in PB-trained monkeys

		CPDD 0043 (mg/kg)				
Subject	PB	Saline	0.3	1.0	1.7	3.0
Ef3	100/1.78	0/4.29	nt	0/3.14	nt	0/3.38
8814	100/1.83	0/1.47	0/1.44	0/1.61	nt	0/1.68
8902	100/1.76	0/1.91	nt	0/1.55	25/0.03*	nr

Data represent the percent drug-appropriate trials/average response rate (resp/sec). The response requirement was FR 5 for Ef3 and 8814 and FR 2 for 8902. CPDD 0043 was administered via nasogastric tube 60 minutes prior to testing. nt=not tested; nr=no responding; *monkey only completed four trials.

Physical Dependence Studies in Hats

When administered to rats undergoing withdrawal from pentobarbital, CPDD-0043 did not significantly reduce behavioral signs of withdrawal, although rats receiving the lower dose did exhibit somewhat fewer signs (see Figure 5). CPDD #0043 failed to prevent the loss of weight associated with that withdrawal, as shown in Figure 6. In fact, the loss of weight was increased slightly in the rats receiving the higher dose (200 mg/kg/day) of the drug.

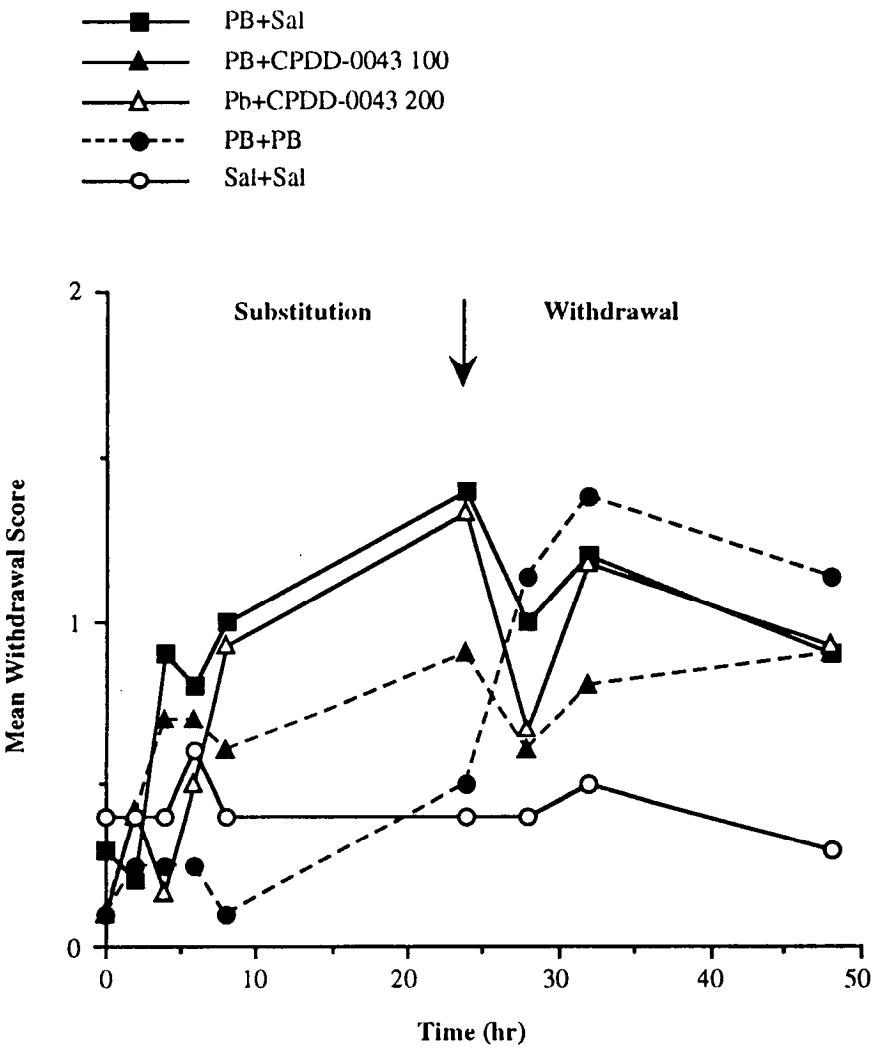


Figure 5. Withdrawal scores with substitution of CPDD-0043 or saline in pentobarbital-dependent rats

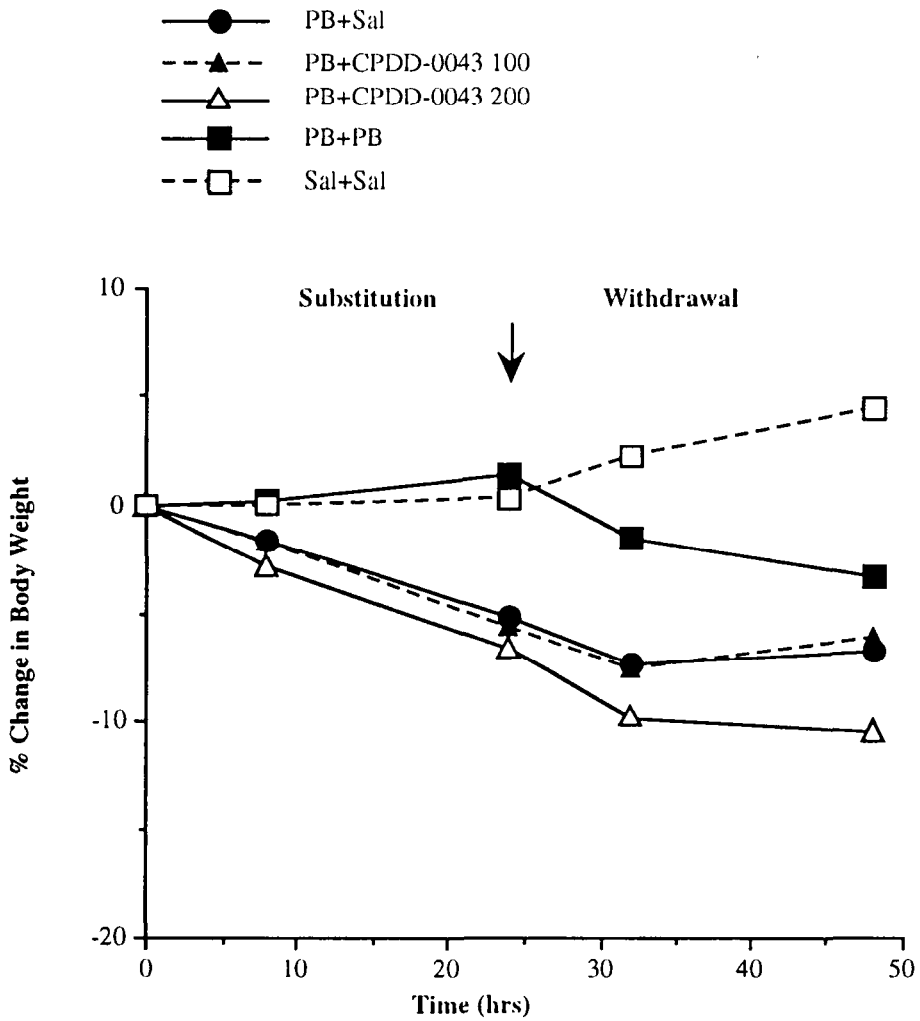


Figure 6. Changes in body weight with substutution of CPDD-0043 or saline in pentobarbital-dependent rats

Potency Estimation in Mice

Spontaneous Locomotor Activity

The effects of CPDD Compound #0043 on spontaneous locomolor activity are shown in Figure 7. The effect of Compound #0043 on spontaneous locomotor activity were not consistently typical of either a stimulant or depressant drug. A mild depressant effect appeared at the dose of 6 mg/kg, but that was the only consistently depressant dose. At the highest dose tested (50 mg/kg) the mice exhibited mild stimulation which lasted for approximately 90 min and was followed by mild depression. Other doses between 1 and 25 mg/kg failed to produce significant effects at more than one time interval.

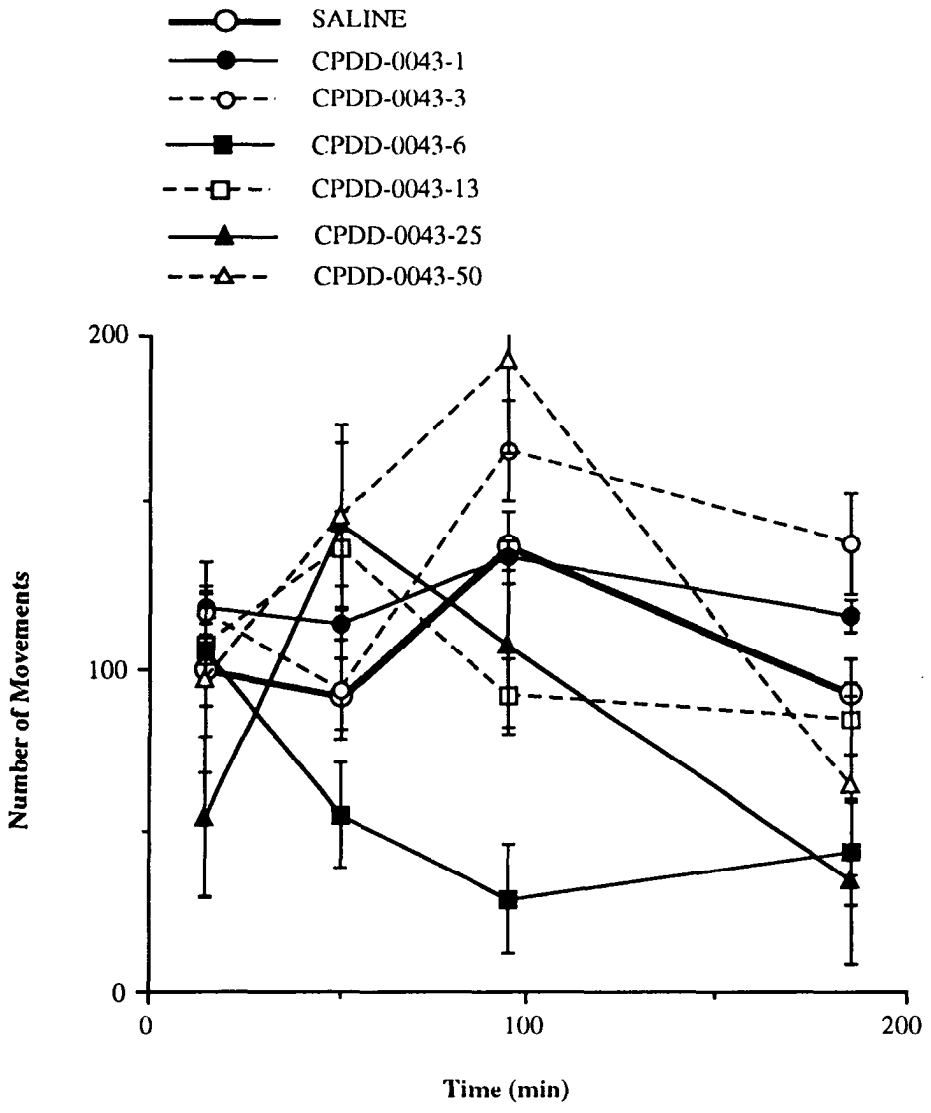


Figure 7. Effects of CPDD-0043 on spontaneous locomotor activity in mice

Inverted Screen Test

Doses of Compound #0043 (1 to 50 mg/kg) produced a dose-related decrement in the performance of this task, as shown in Table 6 below. The effect gradually waned over the period of testing, with the ED-50 increasing from approximately 4 mg/kg at 20 min after injection of drug to approximately 30 mg/kg at 4 hr after injection.

Table 6.
Effects of CPDD compound #0043 on
performance of mice in the inverted screen test

Time alter injection (min)	ED-50 (mg/kg) + (95% C.L.)
20	3.67 (1.69-8.00)
30	5.12 (2.11-12.4)
60	7.46 (3.58-15.5)
120	21.5 (10.7-43.2)
240	33.7 (18.8-60.3)

CONCLUSIONS

CPDD-0042 had reinforcing effects in rhesus monkeys. It produced neither amphetamine-like nor pentobarbital-like discriminative stimulus effects in rhesus monkeys. The monkey that was given a dose of 10 mg/kg in the discriminative stimulus experiment died about 20-30 minutes after administration. When substituted in pentobarbital-dependent rats, it failed to produce a significanl suppression of signs associated with barbiturate abstinence. The greatest effects seen in locomotor studies and the inverted screen test were depressant in nature and lasted about 60 min. At later times and low doses, the behevioral effects appeared to indicate mild stimulation.

CPDD-0042 appears to fit neither the classical profile of a stimulant nor of a depressant drug. The compound would not be expected to prduce subjective effects like those produced by d-amphetamine or PB. The reinforcing effects in monkeys indicate that the compound may have abuse liability, although it appears unlikely to produce dependence of the barbiturate type. The margin between behaviorally active and lethal doses for this compound may be low.

CPDD-0043 functioned as a reinforcer in only one of the three monkeys tested. Although differences frequently are found in the dose that maintains the largest amount of behavior, and in the number of injections taken, the data with CPDD-0043 show differences larger than those usually observed. It produced neither amphetamine-like nor pentobarbital-like discriminative stimulus effects in rhesus monkeys. It did not produce suppression of behavioral signs of abstinence in pentobarbital-dependent animal, and did not prevent weight loss associated with withdrawal in dependent animals. It produced distinct depressant effects on skeletal muscle control as assessed in the inverted screen test, although it did not produce a dose-related diminution in spontaneous motor activity.

CPDD-0043 may provide sedative or muscle relaxant effects. It would not be predicted to produce subjective effects like those produced by either d-amphetamine or PB. The reinforcing effect in one monkey indicates that the compound may have some abuse liability, although this may be limited to some individuals or subgroups of the population. It is unlikely to promote dependence of the barbiturate type.

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SUBJECT INDEX

In order to simplify the Index, the subject subheadings along with page numbers can be found under both the chemical name and the NIH number.

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