National Institute on Drug Abuse

RESEARCH

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Problems of Drug Dependence 1996: Proceedings of the 58th Annual Scientific Meeting

The College on Problems of Drug Dependence, Inc.

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Problems of Drug Dependence 1996:

Proceedings of the 58th Annual Scientific Meeting

The College on Problems of Drug Dependence, Inc.

Editor:

Louis S. Harris, Ph.D.
Virginia Commonwealth University

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IN MEMORIAM

Stanley L. Wallenstein, a member of the College on Problems of Drug Dependence and, for many years, a regular participant in the annual scientific meetings of the former NAS-NRC Committee on Problems of Drug Dependence, died of a cerebral hemorrhage on January 2, 1996. He was 75 years of age - but right up to just before his death, and after his retirement from the Sloan-Kettering Institute in 1991, he continued to be active as a consultant to his former associates at Memorial Hospital and to some in industry on matters relating to clinical analgesic methodology.

Stan Wallenstein may be well remembered by older members of the CPDD as a long-time member of the Sloan-Kettering Analgesic Studies team headed by Ray Houde. Starting as a research fellow in Dr. Houde's lab in 1951, he soon became an important contributor to the controlled clinical analgesic assay methodology which the S.K.I. group pioneered and was noted for. From 1953 onward, Stan Wallenstein was either a co-author or a presenter of the group's annual reports to the NRC Committee on Narcotics and Drug Addiction and later the CPDD, after the committee's name was changed in 1966. Ever since those early years, when the prototypes of most of the now familiar opioid agonists and antagonists were being introduced into medicine, the S.K.I. group's primary interests had been to assist in defining the balance between the desired analgesic properties of these drugs in patients with cancer and their known or suspected abuse liability. Trained as a psychologist, Stan was instrumental in introducing the use of several innovative experimental designs for these assays and he

has been the author on a number of journal articles and chapters in books on the subject of the measurement of pain and assessment of analgesia.

Stanley Wallenstein was a native New Yorker, a graduate of Stuyvesant High School and of City College of New York. He received his postgraduate education at New York University where he obtained his master's degree in psychology. At Sloan-Kettering, he moved up through the ranks to Associate Laboratory member of the Institute by the time of his retirement. Stan was a member of the Lyceum Club of the New York Academy of Sciences as well as a founder member of several scientific pain societies including the Eastern Pain Association, the American Pain Society and the international Association for the Study of Pain.

In addition to his wife, Joan, the only distaff member of the family, Stanley Wallenstein is survived by three sons and seven grandsons - a veritable American League baseball team, complete with a designated hitter - a role which he himself often played at crucial times in the annals of the Sloan-Kettering Institute Analgesic Studies Laboratory.

Raymond W. Houde
Memorial Sloan-Kettering Cancer Institute
New York, New York

COLLEGE ON PROBLEMS OF DRUG DEPENDENCE PRESIDENTIAL ADDRESS 1996: INHALANT ABUSE, A FORGOTTEN DRUG ABUSE PROBLEM

R. L. Balster

Center for Drug and Alcohol Studies and Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

I want to take advantage of the opportunity presented to me to give Presidential remarks for the CPDD to bring to the attention of the College a very important drug abuse problem that has been neglected by the vast majority of drug abuse scientists. It has been referred to by some as "The Silent Epidemic." I would like to discuss four topics concerning inhalant abuse. I want to 1) describe areas of research that are needed, 2) provide some evidence on its prevalence, 3) discuss some of our own research on the acute behavioral effects of abused inhalants and 4) conclude with a brief presentation of public policy approaches to the inhalant abuse problem.

Before going on, you should ask yourselves as the world's preeminent group of drug abuse scientists, "What do I know about inhalant abuse compared to other substance abuse problems?" Do you know about its prevalence and natural history? What types of effects are produced in users? Whether all inhalants produce the same acute effects? Do volatile chemicals differ in their abuse potential, and if so, which ones are most abusable? Which ones the least? How do they work in the brain to produce their acute effects? Does tolerance and dependence develop? Of what type? What are the major toxic effects of inhalant abuse and do substances differ in their toxicity? What are the consequences of prenatal exposure? Have any specific prevention programs been developed for inhalant abuse? Do they work? What about treatment? How many inhalant abusers are there in treatment? Have specific treatment strategies been developed for inhalant abusers? What treatments work best? What is the overall impact on society of inhalant abuse and how does it compare to other substance abuse problems? What policy strategies make sense to minimize adverse effects of inhalant abuse? I believe many of you will not have very good answers to these questions, especially compared to your knowledge concerning other substance abuse problems. There is clearly a need for research on these questions.

Has drug abuse science ignored inhalant abuse? I think so. As far as I can tell, NIDA has less than five research grants that focus primarily on inhalant abuse. At this meeting of CPDD, only two posters, and no presentations, are clearly focused on inhalant abuse research, and both of these are from my laboratory. A casual reading of textbooks and edited compilations of books in the field reveal few that have more than a passing mention of inhalant abuse. Even the National Institute on Drug Abuse, in its last Triennial Report to Congress, failed to include a chapter on inhalant abuse. I cannot blame NIDA for the low visibility of inhalant abuse research. They have sponsored a number of technical reviews, issued requests for applications and have staff persons within the Institute who have focused a lot of attention on the inhalant abuse problem. Here I should mention Dr. Charles Sharp, who over many years has worked to maintain a visibility for inhalants at NIDA.

INCIDENCE AND PREVALENCE OF INHALANT ABUSE

So why do we have so little research on the inhalant abuse problem? Is it because there is a small public health problem? Let me turn to some of the epidemiological data on inhalant abuse in the U.S. and worldwide. These data have been extensively reviewed in a recent NIDA Research Monograph (Kosel et al,, 1995). Data from the Monitoring the Future student surveys for 1994 are representative of recent results from that source (Johnston *el al.,* 1995). Lifetime use of inhalants is just under 20% for 8th, 10th and 12th graders. For 12th graders, this prevalence is just under that of marijuana and more than double that for cocaine. Among 8th graders, lifetime prevalence for inhalant use exceeds that of marijuana use.

Data from the National Household Survey is generally consistent with those from the school surveys in showing a high prevalence among youth 12 to 17, where percentage use in the past year far exceeds use of cocaine and heroin (see below). This Table shows the decreasing prevalence

	1988	1990	1991	1992
Inhalants	3.9	4.0	4.0	3.4
Cocaine	2.9	2.2	1.5	1.1
Heroin	0.4	0.6	0.2	0.1

in cocaine use over the period of 1988 to 1992, whereas prevalence of inhalant use has remained steady. This stable prevalence off inhalant use is somewhat misleading. When rates are looked at separately for abused solvents and nitrites, the rate of. nitrite use has been going down and the rate of solvent use has actually been going up.

I believe that one of the reasons why this extremely high prevalence of use is not accompanied by a larger response from the research community is because most drug abuse treatment providers, at least in the U.S., see only a few cases of inhalant abuse, and other indicators of a large public health impact are relatively low. For example, DAWN mentions for inhalant abuse are far below those for other drugs of abuse and comprise less than 1% of mentions in the DAWN data set. The National Association of State Alcohol and Drug Abuse Directors reports that, among public sector treatment programs, only 0.4% of clients are admitted due to inhalant abuse. The reason for this apparent discrepancy between prevalence data and indicators of public health problems is an important research question.

If some drug abuse experts in the U.S. are not alarmed by the problems of inhalant abuse, this is not true in many other parts of the world where inhalant abuse represents the predominant drug abuse problem, particularly among the most disadvantaged members of society (Kosel *et al.,* 1995). Surveys of street children in Central and South America show inhalant use rates ranging from 27% to 100% (Medina-Mora *et al.,* 1982; Carlini-Cotrin, 1995; Baldivieso, 1995). Space does not allow me to provide many other examples of the worldwide problem of inhalant abuse.

INHALANTS AS A GATEWAY TO OTHER ADDICTIONS

Does the use of inhalants by youth increase their vulnerability to other forms of drug abuse? The answer seems to be clearly, yes. In one study using a secondary analysis of the National Household Survey data (Schütz *et al.,* 1994), inhalant users were found to be 46-times more likely to become an injection drug abuser. For those using both inhalants and marihuana, the relative risk ratio jumps to 86.6 times that of non-users, even after adjusting for a variety of co-factors of this use. In a prospective study of children born in Woodlawn in Chicago (Johnson *et al.,* 1995), inhalant use at age 16-17 resulted in a 9.3 times increased risk for heroin use by age 32.

RESEARCH ISSUES

Given the importance of the inhalant abuse problem, what are some of the scientific issues that need to be addressed by research? People often want to know, why would anybody voluntarily expose themselves to smelly fumes to get high? This question is even asked by drug abuse scientists who seem unsurprised that persons would stick needles into their veins, accept risks of HIV transmission, and engage in all sorts of amazing practices to self-administer cocaine or heroin. Many people also drink bitter liquids to obtain alcohol and caffeine and inhale harsh smoke from burning plants to obtain THC and nicotine. I suppose that this inability to empathize with inhalant abusers comes from the idea that the “high” obtained from inhalants can’t be all that good to justify voluntary exposure. This raises the

question, what is the nature of inhalant intoxication?

Our laboratory research has focused almost exclusively on this question using animal models for the behavioral effects of inhalants. These models are very similar to models which have been so successfully used for studying the acute behavioral effects of other drugs of abuse, except that we arrange for inhalation exposures. The following is a list of some of the research questions we have attempted to answer:

1. What is the nature of the acute intoxication produced by abused inhalants?

2. Is the intoxication similar to that produced by drugs of abuse?

3. Do all inhalants produce the same type of intoxication?

4. Does the type of intoxication produced by abused inhalants determine their abuse liability?

We have compared the acute effects of a wide range of inhalants, and have reached the following conclusions:

1. Solvents can readily be studied using behavioral approaches used for studying drugs of abuse. Inhalants produce concentration-related, reversible, "drug-like" effects on learned and unlearned behavior and produce stimulus effects which can be examined in typical drug discrimination procedures (*e.g.* Balster *et al.,* 1982; Rees *et .al.,* 1987; Bowen and Balster, 1996).

2. Many of the most commonly abused inhalants (*e.g.* toluene and trichloroethane) produce a profile of behavioral and pharmacological effects very similar to that produced by abused depressant drugs, such as the barbiturates and ethanol (Evans and Balster, 1991; Evans and Balster, 1993; Tegeris *et al.,* 1994; Bowen *et al.,* 1996). We believe that, with these abused solvents and anesthetics, abusers are attempting to produce an alcohol-like intoxication.

3. Not all inhalants produce the same profile of effects. For example, we have shown major differences between the depressant-like solvents (toluene and trichlorethane) and the abused nitrtes (*e.g.* Rees *et al.,* 1987). We have also studied a vapor which produces an excitatory profile of effects (flurothyl) similar to that produced by pentylenetetrazol (PTZ) (Evans and Balster, 1992). We also find more subtle differences among otherwise similar inhalants (*e.g.* between toluene and methoxyflurane). We believe that some abused inhalants have a more pronounced excitatory component of their concentration-effect relationship than others.

4. We believe that our research has developed to the point where we can use a battery of test procedures in mice to provide data to help predict the abuse potential of selected inhalants (Balster, 1991).

There are many remaining questions about the pharmacology of abused inhalants which can be answered by animal research. A partial list of these questions would include:

1. What are the cellular bases for their reinforcing effects?

2. Do they produce tolerance/sensitization and/or dependence?

3. What are the effects of combinations of inhalants?

4. What are the effects of combined administration of inhalants and other drugs?

Earlier I listed a wide range of treatment and prevention issues which also deserve research attention. There have even been some attempts to do laboratory-based studies of inhalant effects using nitrous oxide and clinically used anesthetics (*e.g.* Zacny *et al.,* 1994). Since animal studies have shown that abused solvents and volatile anesthetics share many acute effects, using anesthetics for human laboratory research on inhalant abuse seems very reasonable.

TOXICITY

Another important area for laboratory and clinical research concerns the toxicity associated with inhalant abuse. There is a general perception that abusing inhalants is unhealthy, and there are many case reports of adverse health effects, but we need a fuller understanding of the role played by individual inhalants and their combinations found in widely abused products. Animal studies are going to be crucial here to allow characterization of the effects of repeated high-concentration exposures. The main point to make here is that each abused inhalant has its own profile of acute and chronic neurotoxic effects.

Aside from studying acute overdose effects of some abused solvents (Moser and Balster, 1985), we have not been able to do much research on the neurotoxicology of inhalants. One area which we have studied recently concerns the consequences of prenatal exposures. Although there are case reports of adverse effects on children of inhalant abusing mothers, there is little scientific proof that there are teratological effects of solvent exposures. Consequently, we have administered trichloroethane (methyl chloroform), one of the most widely abused solvents, to pregnant mice and evaluated their offspring for behavioral teratological effects. We have found a consistent pattern of developmental delays in the offspring of dams exposed under conditions we believe are relevant to the types of exposures experienced by abusers (Jones *et al.,* 1996). This provides support for the clinical concern for a fetal solvent syndrome.

POLICY MATTERS

There are man) policy issues that merit discussion in mounting a public response to the inhalant abuse problem. There is one feature of this problem that deserves some comment here, and that is the difficulty of using a supply-reduction strategy. Many common products contain abusable inhalants, including household cleaners, paint products, fuels, lighter fluids, etc. Although it may be possible to reformulate some of them or make them more difficult to obtain by teenagers, it seems obvious that the primary effort must be on the demand reduction side. In this respect, the inhalant abuse problem more resembles problems of alcohol and tobacco use, where there are limits to what can be done in supply reduction efforts. This places a special emphasis on the importance of providing effective treatment and prevention. To do this, we need more research in the area of inhalant abuse. My main goal in presenting this issue to members and guests of the CPDD at this plenary session is to try and raise your awareness of research needs and to encourage you to join with the few of us working in this area. This is a problem which affects our nation's youth, and has important world-wide impact. The scientific expertise of you here at this meeting could be a major factor in developing a public health strategy to minimize the harm associated with inhalant abuse. I hope to see more research in this area presented at the next CPDD meeting.

REFERENCES

Baldivieso, L.E. Inhalant abuse in Bolivia. In: Kozel, N.; Sloboda, Z. and De La Rosa, M., eds., Epidemiology of Inhalant Abuse: An International Perspective. NIDA Res Monogr 148:50-63, 1995.

Balster, R.L. Abuse potential evaluation of inhalants. Drug Alc Depend 49:7-15, 1987.

Balster, R.L.; Moser, V.C. and Woolverton, W.L. Concurrent measurement of solvent vapor concentrations and effects on operant behavior using a dynamic exposure system. J Pharmacol Meth

8:299-309,1982.

Bowen, S.E. and Balster, R.L. Effects of inhaled 1,1,1-trichloroethane on locomotor activity in mice. Neurotoxicol Teratol 18:77-81, 1996.

Bowen, S.E.; Wiley, J.L.; Evans, E.B.; Tokarz, M.E. and Balster, R.L. Functional observational battery comparing the effects of ethanol, 1,1,1-trichloroethane, ether and fluorothyl. Neurotoxicol Teratol, in press, 1996.

Carlini-Cotrin, B. Inhalant use among Brazilian youth. In: Kozel, N.; Sloboda, Z. and De La Rosa, M., eds., Epidemiology of Inhalant Abuse: An International Perspective. NIDA Res Monogr 148:64-77, 1995.

Evans, E.B. and Balster, R.L. CNS depressant effects of volatile organic solvents. Neurosci Biobehav Rev 15: 233-241, 1991.

Evans, E.B. and Balster, R.L. Effects of methoxyflurane and flurothyl in mice trained to discriminate pentylenetetrazol from saline. Behav Pharmacol 3:465-473, 1992.

Evans, E.B. and Balster, R.L. Inhaled 1,1,1-trichloroethane produced physical dependence in mice: Effects of drugs and vapors on withdrawal. J Pharmacol Exper Ther 264:726-733, 1993.

Johnson, E.O.; Schlitz, C.G.; Anthony, J.C. and Ensminger, M.E. Inhalants to heroin: A prospective analysis from adolescence to adulthood. Drug Alc Depend 40:159-164, 1995.

Johnston, L.D.; O'Malley, P.M. and Bachman, J.G. National Survey Results on Drug Use from the Monitoring the Future Study. 1975-1994. NIH Publication No. 95-4026, Washington: Superintendent of Documents, 1996.

Jones, H.E.; Kunko, P.M.; Robinson, S.E. and Balster, R.L. Developmental consequences of intermittent and continuous prenatal exposure to 1,1,1 -trichloroethane in mice. Pharmacol Biochem Behav, in press, 1996.

Kozel, N.; Sloboda, Z. and De La Rosa, M., eds., Epidemiology of Inhalant Abuse: An International Perspective. NIDA Res Monogr 148, 1995.

Medina-Mora, M.E.; Ortiz, A.; Caudilo, C. and Lopez, S. Inhalación deliberada de disolventes en un groupo de menores mexicanos. Salud Ment 5:77-86, 1982.

Moser, V.C. and Balster, R.L. Acute motor and lethal effects of inhaled toluene, 1,1,1-trichloroethane, halothane, and ethanol in mice: Effects of exposure duration. Toxicol Appl Pharmacol 77:285-291, 1985.

Moser, V.C. and Balster, R.L. The effects of inhaled toluene, halothane, 1,1,1-trichloroethane, and ethanol and fixed-interval responding in mice. Neurobehav Toxicol Teratol 8:525-531, 1986.

Rees, D.C.; Knisely, J.S.; Balster, R.L.; Jordan, S. and Breen, T.J. Pentobarbital-like discriminative stimulus properties of halothane, 1,1,1-trichloroetbane, isoamyl nitrite, flurothyl and oxazepam in mice. J Pharmacol Exper Ther 241:507-515, 1987.

Schlitz, C.G.; Chilcoat, H.D. and Anthony, J.C. The association between sniffing inhalants and injecting drugs. Comp Psychiat 35:99-105, 1994.

Tegeris, J.S. and Balster, R.L. A comparison of the acute behavioral effects of alkylbenzenes using a

functional observational battery in mice. Fund Appl Toxicol 22:240-250, 1994.

Zacny, J.P.; Sparacino, G.; Hoffman, P.M.; Martin, R. and Lichtor, J.L. The subjective, behavioral and cognitive effects of subanesthetic concentrations of isoflurane and nitrous oxide in healthy volunteers. Psychopharmacology 114:409-416, 1994.

THE NATIONAL INSTITUTE ON DRUG ABUSE: CHANGES, CHALLENGES, AND OPPORTUNITIES IN 1996

A. I. Leshner

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I am very pleased to be at the College on Problems of Drug Dependence's (CPDD) annual meeting, hearing about the many exciting research advances being made. And I am happy to have this opportunity to update you on some of the changes that have taken place at the National Institute on Drug Abuse (NIDA), a few of the policy issues we have been addressing during the past year, and a look at what may lie ahead for the drug abuse research field in the coming year.

For CPDD, this has been a terrific year in Washington. Over the past few years CPDD's efforts to build its Washington presence have become increasingly evident. I believe that under Bob Balster's leadership this organization has really become an integral part of the biomedical science advocacy community in Washington. As a member of CPDD I believe this outcome is advantageous for each of us individually. But I can also tell you that from my perspective as an NIH institute director, it is critical that our scientific community be seen as part of the biomedical research community, and as a part of the advocacy community that represents science at large. It is important for everyone to realize that and to acknowledge the great progress that CPDD has made in this area. In the final analysis, it is, in fact, that advocacy that is reflected in the budget for NIH, and for NIDA specifically.

BUDGET UPDATE

Although we experienced an unusually long period of uncertainty with respect to our budget, the NIH as a whole and MDA did very well in fiscal year 1996, receiving a 4.9 percent increase. For fiscal year 1997, the President's budget request would give MDA a 1.7 percent increase, and the House's figure would provide us with about a 6.4 percentage increase.

Lest you get very sanguine about the positive outlook it is important to remember that the process is not over yet. Nonetheless, our prospects for funding are truly remarkable, particularly within the context of the current fiscal constraints facing the rest of the nation. However, everything is relative. One year when I was acting' director of NIMH, that institute only got a 14 percent increase in its annual budget. And I went home and told my wife that I was a total failure because NIMH had gotten such a meager increase, and everyone was sure that it was because I was an acting director. Let me tell you that we at NIH are totally euphoric about the status of our budget at the moment. And, of course, the positive impact it could have on our ability to meet our obligation to you in the scientific community.

The impact of the various budget scenarios is really very dramatic and very important. Ultimately, what matters most to all of you is the number of grants that we support. And I can tell you that, in recent years, the over all number has continued to rise. Increasingly, we are moving money into investigator-initiated grants. That is our priority. Over the past several years we have moved a tremendous amount of money--over 25 percent--out of the contract line and into the individual investigator line. We are also building our research training programs. We have expanded research training by approximately 75 percent over the last three years. We are attempting to shape our research portfolio, to the extent possible, into one that funds not only more investigators in general, but one that is also moving toward funding younger investigators and more R01 grants. And I think we have been making significant progress in achieving these goals.

One question I am often asked with regard to the budget is how NIDA's funding compares to the other institutes within the NIH. The answer to that question is that, in general, we all rise and fall together. The figures proposed in both the President's request and the House mark-up for NIDA are very close to the NIH

average. One change that has occurred, however, is a slight shift in the way in which the House has laid out the budget with respect to the percentages of money going to AIDS and non-AIDS research.

The main point that I would like to make about the budget is that although the situation at present looks good, we need to remember that it is precarious, and will require the continued support of the budget process.

NEW APPOINTMENTS

We have had a number of new appointments and personnel changes both at NIDA and at the national level that I want to make certain that all of you are aware. Probably the most important single event that has happened to any of us present or to the drug abuse and addiction field at large during the last year has been the appointment of General Barry McCaffrey as the new director of the Office of National Drug Control Policy. Based on my interactions with him thus far I predict that this is going to be a new era of national leadership in the area of drug abuse. Those of you who know me know that I am not prone to hyperbole about our political leaders. But it is clear to me that General McCaffrey understands science, and understands the importance of and the need for research in effectively managing this nation's drug problem. In fact, he has been using one of my lines, "Science needs to replace ideology". I am particularly impressed by the fact that he understands the complexity of drug abuse and addiction and has refused to make any kind of glib promises about a silver, magic bullet, or that we're going to solve this problem tomorrow. In fact, to accomplish his objectives he is asking for a 10 year strategy. I believe that, ultimately, General McCaffrey will be a great advocate for our work, and he will be someone who appreciates and uses the products of our work. His orientation to dealing with the problem and his support for the efforts in which we are engaged is certain to benefit the field of drug abuse research.

I also want to acknowledge the continuing leadership provided by my colleague, David Mactas, Director of the Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Substance Abuse Treatment (CSAT). Our organizations have continued to work very closely together on a variety of issues during the past year and we have an interagency Workgroup comprised of staff from both NIDA and CSAT that meets regularly to generate and coordinate ideas for further collaborative activities.

Within NIDA, Timothy Condon, Ph.D., has recently been named the institute's Associate Director for Science Policy, and Director of our Office of Science Policy and Communications (OSPC). Barry Hoffer, M.D., Ph.D., a neuropharmacologist from the University of Colorado's Health Sciences Center, will join NIDA in the fall as the institute's Scientific Director and the Director of our Intramural Research Program (IRP) at the Addiction Research Center in Baltimore. I think I announced last year that Steve Zukin, M.D., formerly a professor of psychiatry and neuroscience from the Albert Einstein College of Medicine of Yeshiva University, is now the Director of our Division of Clinical and Services Research (DCSR). Charles Grudzinskas, Ph.D., left his position as Director of NIDA's Medications Development Division (MDD) and has gone back to industry. And Frank Vocci, Ph.D., who has been providing outstanding leadership for a long time as MDD's Deputy Director is now serving as Acting Director. Harry Haverkos, M.D., who has been serving as Director of our AIDS office has decided that he would like to be more directly involved in conducting research and has recently joined the IRP to help in shaping their program related to HIV/AIDS. Steven Gust, Ph.D., who had been serving as Deputy Director of the AIDS office has now assumed the role of Acting Director and has been doing a spectacular job, particularly in the very important task of interfacing with NIH.

I also want to mention two branch chief appointments that have occurred recently. Joseph Frascella, Ph.D., has been named Chief of the Etiology and Clinical Neurobiology Branch of DCSR, and Henry "Skip" Francis, M.D., is the new Director of DCSR's Clinical Medicine Branch.

And I want to take this opportunity while everyone is here to thank George Uhl, M.D., Ph.D., for his outstanding service as Acting Scientific Director. We at NIDA are grateful for the enormous personal sacrifice

he has made and the exceptional leadership that he has provided for the Intramural Research Program over the past two years.

NIDA COUNCIL RESTRUCTURING

This year NIDA has changed both the structure, and, to some extent, broadened the function of the National Advisory Council on Drug Abuse. We have expanded the number of council members by 50 percent and have folded in some of the members of what once was known as our Extramural Science Advisory Board. This new advisory group has been and will continue to play a more extensive role in setting NIDA's policies and priorities. For example, over the course of the last year, our council has taken up a number of emerging issues of concern to all of us. Because I feel it is extremely vital for everyone in the field to understand these issues and where NIDA stands on them, I want to touch briefly on a few of the more critical ones.

One key issue that has emerged relates to NIDA's research center grant program. In an effort to help ensure that the centers established and supported by NIDA are able to accomplish the purpose for which they were intended and that this type of grant mechanism is being utilized most appropriately NIDA undertook an in-depth review of its existing center grants portfolio this year. We established a council subcommittee to assist us in looking at all of this information and to aid us in formulating some of the methods that could help our program evolve in the direction we want it to go. The end result has been the development and dissemination of a set of very explicit guidelines for the creation and maintenance of NIDA's research centers program. A notice stating the availability of these guidelines was published in the NIH Guide for Grants and Contracts on September 22, 1995. These guidelines are also on NIDA's Homepage on the worldwide web if you want to access them that way.

A great deal of effort has been focused this year, both by NIDA staff and by our Council members, on refining our definitions of AIDS and non-AIDS research. The issue of what is AIDS and what is not AIDS, and what is AIDS-related and AIDS-focused is one that NIDA and other institutes at NIH have had to wrestle with for some years. NIDA has repeatedly dealt with this set of issues particularly as they relate to our budget. One recent NIH activity that has drawn increased attention to the need for clarification is the work of the panel of outside researchers, charged by the NIH Office of AIDS Research (OAR) with evaluating NIH's AIDS program. And so, we at NIDA, with the help of outside experts and the members of our Council have laid out our definitions. We also have listed different kinds of areas of research in six sub-categories which were chosen to correspond to those of the NIH's OAR for the last several years. These categories include epidemiology and natural history, etiology and pathogenesis, vaccine development, therapeutics, treatments for HIV infection, behavioral research, and information dissemination.

A third issue that the Council has been very active in helping us with and one that I think is tremendously important has been the ongoing discussion of our grant peer review, and the integration of our existing review structure into the NIH-wide system. At the last council meeting in May, the members passed a statement of principles that has been sent to all of the leadership. This document lays out general principles under which that integration should occur. The Council has also compiled a survey which is being circulated here at the CPDD meeting. And what they are asking of all of you is to articulate for them your major concerns about the integration of peer review. I would like to encourage you to get that form, complete it and return it so that we can collate all of the input we receive and make some decisions based on your views.

Overall the efforts and insights of our council members have been enormously valuable in helping us to address and resolve a wide variety of policy issues. And we intend to continue to solicit their help as other topics emerge.

MESSAGE OF THE YEAR

Finally, every year I am compelled to come up with some message. My first message as NIDA director was, I've got a secret. Last year I spoke about what I see as one of NIDA's major challenges and one which needs to be faced by all of us who work in the drug abuse field--to bridge the "unique disconnect" that exists between the scientific facts and the public's perception about drug abuse and addiction.

This year, the message I want to convey is that in order for the field to continue to thrive as it has been doing, we need to go public with our science. Although I am delighted that we in the drug abuse scientific community now know more about drug abuse and addiction and what to do about these problems than we ever have in our history, the problem is that we are still guilty of keeping too many of the promising research advances that are taking place a secret. In essence, my message is a continuation of an earlier theme. It is true that we know a tremendous amount. That is terrific. But as I have said before, we are the only ones who seem to know about it.

There is this "disconnect" that I spoke about last year between the public's perception of drug abuse and addiction and what we in the scientific community know through our research. You may remember the conceptualization of scientific knowledge going one way while public perception is chugging along in the opposite direction. In order to make progress in destigmatizing addicts or in increasing the credibility of our science all of us must work together to bridge this disconnect.

What this means is that all of you need to go public with your science. We have got to stop entertaining ourselves--and I don't know a more subtle way of phrasing it. We at the National Institute on Drug Abuse and many of the scientists we support have had a phenomenal year in the press. We have prepared close to a dozen major press releases announcing research findings and their practical implications. The media attention that these findings have generated has, in turn, provided great support for the budget. Our success has had a tremendous effect on destigmatizing drug abuse and addiction, and helping to educate practitioners and policy-makers.

I want to make it clear that you have a major role and obligation in educating the public. You can not just depend on us to do it for you. All too often we hear about great findings after they have been published. But when they have reached that stage they are no longer of any use to the press. Great findings are only of interest to the press if they get advance notice. So, you have to tell us about your findings--in advance. And it is especially important that you acknowledge the source of your research support. If you do not, you are ultimately hurting the field since NIH/NIDA funding adds to the credibility of the research.

We have recently issued a policy at NIH that requires those of you who are NIDA grantees to explicitly acknowledge NIH and NIDA in publications generated through the Institute's support. Our most staunch supporters in Congress are also strong advocates for getting the science out. I will tell you that Mr. Porter, our biggest friend on Capitol Hill, is constantly telling us how critical it is to relay our research findings to the public.

When I was a bench scientist, it was considered crass to talk publicly about our science--or to get it in the newspaper. In some respects it was then considered beneath us. But over the years, attitudes have changed. Now it is no longer crass to educate the public about promising scientific advances--it is critical to the vitality of the field. If you want to know where to relate your findings, I urge you to go to either your program officers or to NIDA's press office for assistance or advice. Or, if you would prefer, you can send announcements to me by E-mail; my new E-mail address is very simple--*all6m@nih.gov*. We will work with you to develop press announcements. However you choose to do it, it is extremely important to let the public know about these saving advances that are going on. And we need to impress upon the public why they should care about the progress that is being made. It is not just entertaining. We need to help the public understand that our science is at last at a level where we can use it in a concrete way to get a handle on drug abuse and addiction.

Much of what has prompted my message for this year came from listening to Ed Sellers' talk last year. He showed the great disparity that exists between the true nature of addiction and the public's understanding of this condition. And even more alarming, there is also misunderstanding within the health professions. I found the implications of Dr. Sellers' data very depressing. We must increase our efforts to change the way that drug abuse and addiction and those it afflicts are perceived. So, this year's exhortation is, let us try to work together on the problem.

We at NIDA have been working very hard over the past year to bridge the "disconnect." We've had "Town Meetings" in various places across the country from Anchorage, Alaska to Tampa, Florida trying to increase the public's understanding and dispel the myths that are obstructing our progress. Other fields of medicine that have dealt with stigmatized diseases have been successful in changing public opinion. For example, I want those of you who are old enough to think back to when having cancer was stigmatized. Forty years ago, no one in this country died of cancer--they died of a long, protracted illness. The mental health field has also come a long way in changing the public's view of several mental disorders. For example, when I was a graduate student schizophrenia was thought to be the result of being raised by schizophrenogenic mothers and refrigerator parents. Aging is another example. People did not used to age or suffer from Alzheimer's disease. Use of the science system was tremendously effective for increasing our understanding about many other health issues. It is crucial that we use the scientific underpinnings of drug abuse and addiction in the same way. In my view, each of us in the scientific community has a responsibility to make sure that what we do is not just entertainment, not just our efforts to answer interesting questions, but efforts that are directed at fulfilling an urgent public health need.

INTRODUCTION OF THE NATHAN B. EDDY MEMORIAL AWARD

J. H. Jaffe

It is an honor and a personal pleasure for me to introduce Griffith Edwards, the recipient of the 1996 Nathan B. Eddy Award.

Griffith Edwards was born in India in 1928. His family returned to England when he was quite young and he was educated there. He received a number of prizes for scholarship, and his later academic qualifications are formidable. Although he entered Balliol College, Oxford, on a mathematics scholarship, his interests soon turned to physiology and anatomy. He earned what he assures me are the usual three degrees and went on to study medicine at St. Bartholomew's Hospital Medical College and psychiatry at the Institute of Psychiatry at the Maudsley. He earned a Doctorate in Medicine from Oxford in 1966, and the D.Sc. from the University of London in 1990 - not coincidentally, the same degree his father had earned there almost 70 years earlier.

At present, Griffith Edwards is Professor Emeritus of Addiction Behaviour at the Institute of Psychiatry at the Maudsley. Until he retired in 1994, he was Director of the Addiction Research Unit at the Institute of Psychiatry and Chairman of the National Addiction Centre. These titles, however, do not convey the true influence of today's awardee. Griffith Edwards was the driving force behind the establishment of both the Addiction Research Unit and the National Addiction Centre. For more than a quarter century he has provided the energy, intellect, and vision that have led and inspired an entire generation of researchers who studied and worked there. Just as, in the 1950s and 1960s, the Addiction Research Center at Lexington and its scientists nurtured many of our now senior addictions researchers, the Addiction Research Unit and Griffith Edwards did so in the 1960s and 1970s for many of the current generation of addictions researchers in Great Britain, Australia, and other countries throughout the world. It is worth noting that the title "Professor of Addiction Behaviour" was created specifically for him and, in 1979, he became the first person in the U.K., if not the world, to hold it.

Griffith Edwards belongs to a marvelous British scholarly tradition of descriptive psychiatry and epidemiology. He has long been interested in better defining the subtle boundaries between drug/alcohol use, misuse, abuse and addiction. His passion for careful observation also places him strongly in the tradition of Nathan B. Eddy. It was careful observation that led Griffith to develop (with Milton Gross) explicit criteria for defining alcohol dependence along a continuum of severity which allowed for differentiation between dependence severity and drug-related disability. This work led to studies of clinical outcome that highlighted the importance of understanding and quantifying severity of dependence as a predictor of outcome of treatment and of natural recovery. The current psychiatric nosology built into the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III and DSM-IV) and the World Health Organization's International Classification of Diseases (ICD-9 and ICD-10) describes drug dependence as a syndrome varying in severity. This definition is directly derived from Griffith Edwards' work.

Griffith's research has ranged from clinical psychopharmacology to hypnosis, and from epidemiology to cross-national studies of alcohol policy. In the area of treatment for alcoholism, Griffith Edwards is perhaps best known for his pioneering random assignment study comparing the effectiveness of standard treatment to simple advice, and for subsequent follow-up studies. These studies, which showed that even brief encounters with medical advice and admonishments can have positive impact, have profoundly influenced the way policymakers and clinicians think about dealing with alcohol abuse. A multi-site cross-national study has demonstrated that brief interventions in problem drinking can produce significant decreases in alcohol consumption. Through his own early studies and, equally, by recruiting and supporting at the ARU scholars such as M.A.H. Russell, Griffith Edwards has also greatly influenced research on nicotine dependence and its treatment. And in yet another distinct area, Griffith encouraged and collaborated with Virginia Berridge work on the history of opiate use in Great Britain - work which allow us to see present policies in their social context. His work in the U.K. and with the World Health Organization on alcohol and drug policy points out the importance of supply

and availability of alcohol as determining factors in the prevalence of alcohol problems. The significance of this work has been recognized by his peers as well as by the numerous governments to which he has provided consultation.

I first became aware of the depth and breadth of Griffith Edwards knowledge and understanding of the complexity of individual, cultural, and national responses to psychoactive drug use when Dale Cameron asked us, in 1970, to draft a working paper for a meeting of the World Health Organization Expert Committee on Drug Dependence. Our paper emphasized both the notion of a complex, dynamic system influencing drug use, control, treatment, prevention, and research, and the need for coordinated national responses. It also stressed the need for gathering data that permit judgments to be made about the impact of those responses. The inevitable workings of the committee process largely whittled away the elegance of Griffith's prose, but the notion of a national response survived in the report. The vice-chairman and unquestionably the dominant personality of that WHO Expert Committee meeting was Nathan B. Eddy.

Four months after that meeting, many of Griffith Edwards' ideas were incorporated into a report that several CPDD members and I prepared for the White House staff, in which we recommended that the United States government should develop a coordinated national strategy on drug abuse. The U.S. National Strategy document that is now promulgated annually, and which was intended to force those charged with that responsibility to think seriously about how to allocate resources, had its beginnings in Griffith Edwards' ideas on how to view the problem.

Griffith's seminal contributions in the areas of nosology, policy, and treatment are products of an extraordinary intellect and critical thinker. He is the author or editor of more than 28 books and more than 150 research papers. Yet, he has made an equally important contribution to the field in his role as teacher. For almost 20 years, as Editor of, Addiction, (formerly the British Journal of Addiction), which is the oldest continuously published scholarly journal in our field. Griffith Edwards has been a mentor and teacher to researchers, clinicians, and policymakers all over the world. He has been a consultant to governments on four continents; as a member of the World Health Organization Expert Committees and of the Council of Europe Workgroup; he has been an informal consultant to numerous others. Griffith is everyone's first choice to chair a committee or Workgroup that is charged with producing a thoughtful, articulate report. Two important reports issued by the Royal College of Psychiatrists in the 1980s, one on alcoholism and one on drugs, were largely authored by Griffith Edwards and are, in my opinion, classics of thoughtful analysis combined with elegant, lucid prose.

It is not surprising, of course, that Griffith Edwards has received honors and awards from numerous learned societies and organizations in several countries. Included among the prestigious awards is the Jellinek Memorial Prize. In 1992, the Faculty of Medicine of the University of Chile awarded him an Honorary Professorship with life tenure. (Griffith has asked me to refrain from reciting further from the extensive list.)

Along with all of his scholarly and international activities, for more than 25 years Griffith has continued to directly supervise a clinical inpatient alcohol treatment unit at the Bethlehem Royal Hospital and an outpatient service at the Maudsley, where he has directly mentored a number of outstanding registrars (residents in psychiatry) who have gone on to make noteworthy contributions to the field.

In this seeming diversity of interests there is profound coherence. In striving to show how all of the various elements affecting drug use are essential to understanding the nature of addiction, Griffith Edwards emphasizes the relationships among the phenomena, bridging and bringing together the relevant disciplines that contribute to that understanding.

Griffith will touch on this theme in his address today, which is entitled "Lunch with Dr. Kerr," but let me give you the flavor of his approach by quoting from a WHO Memorandum on terminology, the product of a Workgroup chaired, not surprisingly, by Griffith Edwards. The passage is taken from a section of the document that begins, "Where is dependence located in this model?"

> We prefer to argue that dependence is essentially located within a system, and in this context we regard a syndrome as a rather simple translation of the concept of a system... Others might prefer to see dependence in terms of what is going on within the individual, either physiologically or psychologically, or strictly in terms of behavior alone, or in terms of the social role that the drug user assumes. We believe that a system or syndrome model that seeks to take account of the interactions between drug, person, and environment is much to be preferred. Any interpretation that places too much emphasis on only one part of the whole system is imperfect and misleading. (Edwards *et al.,* 1981, p. 232)

There are many parallels between Griffith Edwards' professional interests and his personal life. It is not surprising that he places highest value on the personal relationships and friendships he has formed over the years with professional colleagues all over the world.

Griffith Edwards, for your seminal contributions to the field of addiction, and for the mentoring and friendship you have generously bestowed on so many of us, the College on Problems of Drug Dependence salutes you with the Nathan B. Eddy Memorial Award.

Selected References:

Edwards, G., Arif, A., Hodgson, R.: Nomenclature and classification of drug- and alcohol-related problems: a WHO Memorandum. *Bull. World Health Org.,* 59(2):225-242, 1981.

Edwards, G., Gross, M.: Alcohol dependence: provisional description of a clinical syndrome. *Brit. Med. J.* 1:1058-1061, 1976.

Edwards, G., Orford, J., Egert, S., *et al.:* Alcoholism: a controlled treat of "treatment" and "advice". *J. Stud. Alc.* 38:1004-1031, 1977.

Royal College of Psychiatrists: Drug Scenes: A report on drugs and drug dependence by the Royal College of Psychiatrists. Gaskell: London, 1987.

Royal College of Psychiatrists: Alcohol & Alcoholism: The report of a Special Committee of the Royal College of Psychiatrists. Tavistock Publications: London, 1989.

WHO Expert Committee on Drug Dependence: *Wld Hlth Org. tech. Rep. Ser.* 460: 1970.

LUNCH WITH DR. KERR: NATHAN B. EDDY AWARD LECTURE

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Let me start by expressing my deep sense of gratitude for the honor the CPDD does me in conferring the Nathan Eddy Award. It is also an occasion on which it is proper to record my profound awareness of what we who work in other parts of the world owe to the energy, inventiveness and brilliance of the American research contribution to the alcohol and drug field. I have reason to be grateful to your country not only for what it has given me in terms of the science itself, but also through the rich benefit of personal friendships that have come to me as a result of these scientific contacts. Thus, the sense of honor and pleasure in receiving your award is much intensified by the fact that the person introducing me to this meeting is my very good, long-time and esteemed friend, Jerome Jaffe (Jaffe 1965, 1987, 1995), from whose wisdom and kindness I have benefited these many years. So, to my talk.

On April 25, 1884, the inaugural lunch of the British Society for the Study and Cure of Inebriety took place in the rooms of the Medical Society of London. Held in a prestigious setting which must immediately have given stamp of authority to the newly formed society, the occasion attracted nearly 100 medical practitioners and the presidents of four medical societies. There was also present a rich sprinkling of the good and the great, including the 84 year old Earl of Shaftesbury, a noted social reformer who had in his day worked with Florence Nightingale. However, although lay people could be associate members, only medical practitioners could enjoy full membership of this organization.

With lunch served and no doubt heartily enjoyed (our Victorian ancestors expected a table to be well victualled), Dr. Norman Kerr gave his inaugural address. That speech marked a defining moment in late 19th century medical thinking on the nature of the drink problem. It was a founding statement by the widely respected president and moving spirit of this newly established society which had as its aim "to investigate the various causes of inebriety and to educate the professional and public mind to a recognition of the physical aspect of habitual intemperance."

Having some personal investment in what Dr. Kerr said all those years ago when he pushed back his chair, it is only right to declare my interest. The published Proceedings of the Society for the Study and Cure of Inebriety began to appear in 1884, but in 1887 the word "cure" was dropped from the title of the Society and its Proceedings. In 1903, the Proceedings were transmuted into a journal, the ***British Journal of Inebriety,*** while in 1946, the word "inebriety" was traded in for "addiction" and the journal became the ***British Journal of Addiction to Alcohol and Other Drugs.*** In 1993 the journal changed its name to ***Addiction,*** plain and simple, and that is its present title.

And the personal interest to be declared? In 1884, Norman Kerr was not only the first president of a learned society which remains in active existence to this day as the Society for the Study of Addiction, but Kerr was also the *de facto* editor of the Society's journal (or Proceedings), a position which he held for 15 years. A scholarly and informative, history of the Society has been provided by Virginia Berridge (Berridge 1990). My interest in what this founding father said in 1884, derives from the fact that I have since 1977, had the privilege and responsibility of editing the publication which Kerr initiated, bear him affection, and not infrequently find myself seeking his approval of the editorial policies which my colleagues and I are today pursuing for a journal which has been in continuous publication for 112 years. That journal is now committedly international rather than British, has regional offices and editors in the USA (Dr. Thomas F. Babor) and Australia (Dr. Timothy Stockwell). We have subscribers in more than 50 countries. But how does the content of today's journal and what the international scientific world writes and we publish in 1996, relates to anything that Dr. Kerr said in

1884, after lunch, at the rooms of the Medical Society of London? If we could perform a content analysis of his address, we might discern continuities and discontinuities and gain insight into the roots of our present beliefs and concerns and the nature of dilemmas which still face us. Wouldn't it have been interesting to have had someone taking notes at that lunch, even if 1884 was some years too soon for a tape recorder?

I am, of course, setting this up. We can precisely answer the question as to what was said at that inaugural lunch. The Presidential address was published as the first paper in the first volume of the Society's Proceedings (Kerr 1884).

Let's first reproduce the opening paragraphs of this transcript so that we can taste the prose style in which the message was embedded. Kerr had been a journalist before he took up medicine (Crothers 1906) and he was fond of the oratorical flourish, and would often embellish his text with a line or two of quoted poetry.

> Whence comes this nameless, this indescribeable, this unfathomable load of inebriety? It does not like a destroying angel swoop down upon the earth from without and gather in its spoils of destruction and woe in 'A bewildering mist of horror'. Whence comes this inebriety? And under what conditions? (Kerr 1884, p.2)

And he immediately provided a categorical answer to his own question and identified the essential premise for the disquisition which was to follow.

> Inebriety is for the most part the issue of certain physical conditions, it is an offspring of maternal parentage, is a natural product of a depraved, debilitated, or defective nervous organization. Whatever else it may be, in a host of cases it is a true disease, as unmistakably a disease as is gout or epilepsy or insanity . . . (Kerr 1884, p.3)

Thus inebriety was declared roundly and unequivocally to be a disease, a brain disease, and this more than half a century before the founding of the Yale Center of Alcohol Studies, and 76 years prior to the appearance of Jellinek's "Disease Concept of Alcoholism" (Jellinek 1960).

Let me explain the way in which I propose that this talk should now proceed. First, I will put before you something of what Kerr said in his 1884 address. I will then say a little about Anglo-American relationships at that time and will suggest that Kerr's views were not just British or parochial but represented a contemporary Anglo-American expert consensus. Next I will try briefly to identify what we might see as the long term, present and indeed future consequences of two seemingly contrasting models as to the nature of the drink problem being made available to society in the latter part of the nineteenth century. The model which Kerr articulated of alcoholism as a brain disease which affected some persons as being the problem, was radically different from the Temperance analysis which had the mass impact of alcohol on the population as the problem. 1884, I will argue, is still with us.

WHAT KERR SAID

It is possible to discern a set of themes which constituted the Kerr's framework of thinking and we can for convenience order the content of his presentation under four headings.

Inebriety is a disease caused by an abnormality in brain function and characterized by craving

The following passage elaborates on Kerr's opening statement and illustrates his uncompromising stance on this point:

> I have not attempted to further dogmatize on disputed points as to whether inebriety is a sin, a vice, a crime, or a disease. In my humble judgement it is sometimes all four, but oftener a disease than anything else, and even when anything else, generally a disease as well . . . in all indulgence in intoxicants there is a physical influence in operation, a physiological neurotic effect, the tendency for which is to create an appetite for more of the intoxicating agent. (Kerr 1884, p.14)

As regards the criteria which he saw as defining the existence of this condition, Kerr put emphasis on craving:

> What is inebriety? We may define it as a diseased state of the brain and nerve centers, characterized by an irresistible impulse to indulge in intoxicating liquors or other narcotics for the relief which they afford at any peril.. (Kerr 1884, p.3)

Multiple causation

Kerr identified a number of possible causes of inebriety:

Genetic predisposition

(i) I have no doubt that at least 30 per cent of bad cases of inebriety owe their origin mainly to an inherited alcoholic taint . . . Not only is there hereditary transmission of the drink crave itself, which needs only the slightest sip to be aroused in full force, but there are also transmitted the pathological conditions, the abnormal changes wrought by alcoholic inebriety. (Kerr 1884, p.4)

Kerr's concept of heredity thus appears to have included a Lamarckian element.

(ii) Nervous shock. Inebriety might be brought on by shock occasioned by losses in business, bereavement, or disappointment in love. Whatever the immediate vehicle for the nervous shock the common underlying element was "some obscure pathological disturbance by deranging the functions of the nervous system, setting up a cerebral or nervine paralysis, or it may be an irritable state of the brain which calls for an intoxicant or other narcotic as a solace for unbearable suffering." (Kerr 1884, p.5)

(iii) Overwork. "Overwork" said Kerr, "is a fertile cause of inebriety". He had in mind not the plight of the labouring classes but what he referred to as "the overtaxed thinker":

> The clergyman, the Christian worker, or the physician after an exhausting day spent, O, how wearily! in listening to long dreary accounts of innumerable wrongs and ailments, imaginary and real, is so prostrate that he cannot even look at the food which his badly used stomach so strongly needs . . . An intoxicating stimulant in a few seconds dispatches every sense of fatigue, seems to infuse new vigor into his veins, new life into his fainting spirit. (Kerr 1884, p.5)

A closely related cause likely to be encountered "in this high-pressure age of work and worry" was "absence of amusement".

(iv) The medical prescription of alcohol. Kerr recognized iatrogenic alcohol dependence as a problem of the time.

> The story is too sad to be told of the frank, noble-hearted, abstinent women whom I have known to be launched on the troublous and fatal sea of confirmed inebriety by the mistaken prescription of strong drink while nursing. (Kerr 1884, p.7)

(v) "The habit of drinking long continued". In one short paragraph Kerr considered the possibility that drinking per se might be a cause of the postulated brain disease:

> Though this has been disputed, I think there can be little doubt that a predominating factor has been the habit of drinking long continued. Whether the drinking has been 'moderate' or 'free', or 'excessive', the habit has not necessarily been vicious. (Kerr 1884, p.8)

(vi) Other and miscellaneous causes. Among other and miscellaneous identified causes were head injury, fevers, tuberculosis, syphilis, insanity, and among women sexual excitement:

> Sex exerts a potent influence, nerve storm in natural function being an influential factor in the production of inebriety among females. (Kerr 1884, p.7)

Kerr on treatment

Kerr insisted that the treatment goal should without exception be total and lifelong abstinence.

> No exceptions to this rule, social or ecclesiastical, can be permitted without serious risk . . . From unacquaintance with this fact, reformed inebriates have been led back to their former evil course of intemperance by tasting their intoxicating bane at communion . . . while life is, many a rescued one dare not even sip the weakest form of such drinks. (Kerr 1884, p.8)

Moreover, it was essential to involve the inebriate in his own cure by explaining to him "that he is suffering from a physical disease, like a man afflicted with rheumatism or sciatica, and that his hope of permanent cure lies mainly in recognizing his physical susceptibility to the action of a poisonous narcotic material agent" (Kerr 1884, p.9).

The rational next step in the treatment process was to remove whenever possible the underlying cause. An illustration Kerr gave of such a rational approach provides a period piece of Empire:

> An inebriated patient of mine, a tall, strong, well-built man, aged 46, had suffered from heat-apoplexy in India, and was so affected by the heat in London that in two different summers he became insane from drinking and had to be put under restraint for a couple of months at a time. He succeeded at length in keeping free from drink and from an insane outbreak by adopting the plan of, during the hot season, restricting himself to a plain non-heating diet, by adopting suitable clothing, and by wearing headgear, which kept his head cool. (Kerr 1884, p.7)

In most instances a fundamental element in the treatment plan would however have to be a prolonged separation of the inebriate from their drink and this would probably necessitate admission to an institution: the newly formed society campaigned vigorously over the ensuing years for a strengthening of legal provisions for compulsory detention. The supposed rationale which supported this favouring of institutional confinement as the foundation for the treatment of inebriety, lay in the belief that brain disturbance needed time to recover: "There has been a degeneration of brain tissue, and time must be given for a new and ample supply of healthy brain and nerve substance." (Kerr 1884, p. 10).

Forward together under the banner of science

Under his final heading of "Concluding appeal" Kerr briefly considered prevention. He declared, "By all means use every moral and legislative effort in your power to mitigate and prevent intemperance and the prolific mischief flowing therefrom." He commended the work of the Bands of Hope. However, he then went back once

more to emphasize the need for science which could be directed at the cure of inebriety, and science was very much to be nailed at the Society's masthead.

> We confidently believe that we will succeed in acquiring a more exact acquaintance with the phenomena, causation and condition of inebriety, by engaging in study of this intractable disease with the same strictly scientific method with which we enter upon the study of other forms of disease. (Kerr 1884, p.15)

Such an agenda was seen as having a capacity to unite all parties in common endeavour and thus bring together "makers, the distributors, and the users of strong drink", with "the moral suasionist, the teetotaller and the prohibitionist". In a final, rousing forward-together appeal put to this after-lunch audience, Kerr declared:

> This is a Society for the study and cure of inebriety. Permitting no preconceived opinions to stand in the way of our research, allowing no foregone conclusions or sentiments to bias our judgement, we propose, without prejudice or passion, deliberately and persistently to pursue our modest inquiry, in the earnest hope and confident anticipation that in the solution of the dark and perplexing drink problem we, or our successors, may are long be rewarded with . . . (Kerr 1884, p.16)

And here as a final flourish he offered some lines of poetry. Science, he confidently averred, would in due time reward his audience with:

> Truth unbroken and entire;
> Truth in the system, the full orb; where truths
> By truths enlightened and sustained, afford
> An arch-like strong foundation to support
> The incumbent weight of absolute, complete
> Conviction; here, the more we press we stand
> More firm. (Kerr 1884, p.16)

Heady stuff, and we may confidently assume that the ensuing vote of thanks was cheered to the echo.

That acclamation would have been justly earned. Kerr had undoubtedly put before his audience a comprehensive statement on the nature of the drink problem immensely congruent with the spirit of the then contemporary medical world - entrepreneurial, optimistic, reductionist, frequently getting ahead of the evidence and biologizing or neurologizing what it could not understand, haunted by fears of national degeneration, and entertaining few doubts. In an age when diseases were the target and their pathological or bacteriological basis the question, inebriety was given ranking with "gout or epilepsy or insanity". The shared and unifying task put before Kerr's audience was defined as that of discovering the scientific basis for this disease in brain function.

Let's try at this point to summarize matters thus far and encapsulate what Kerr was saying. Inebriety was a disease and his intuitive guess was that its pathology lay in inherited or acquired brain disturbance. He identified craving as the pathognomonic feature of this disease. He stated that craving could be cued by further drinking even after prolonged abstinence. The possible causes of this disease were multiple and included genetic predisposition, adverse life events or fatigue, and "drinking long continued". Total abstinence had to be the treatment goal. Kerr was in large measure building on and integrating the ideas of earlier authors such as Benjamin Rush (1790), and Thomas Trotter (1804) and the idea of drunkenness as a disease was common among doctors in the 18th century (Hirsh 1949, Porter 1985). It would be wrong to see him as uniquely prescient, but it was the synthesis which was exceptional. What he articulated after that lunch sums up the outlines of a model which probably still drives much present-day research on alcohol dependence and provides the working model for the practice of many modern physicians. That's quite some prescience.

Kerr, the Society and the Anglo-American connections

Thus far we have focused this discussion on the significance of the inaugural address delivered in 1884 by the President of a British and London-based organization. What needs to be emphasized is that British and American thinking on inebriety were at this time moving in much the same direction, with a shared emphasis on the disease concept and the necessity for institutional treatment, but with America somewhat leading the field so far as the foundation of societies and journals was concerned.

The first and highly influential American institution for the treatment of inebriates was the New York State Inebriate Asylum at Binghampton, NY, and by the 1890s there were more than 30 inebriate treatment institutions of varied type operating in the USA (American Association 1893). The American Association for the Study and Cure of Inebriates had been inaugurated in 1870 and its Articles of Association amply confirm a commitment to the disease model and to campaigning for institutional care:

1. Inebriety is a disease.
2. It is curable as other diseases are.
3. The constitutional tendency to this disease may be either inherited or acquired; but
4. The disease is often induced by the habitual use of alcohol or other narcotic substances...
5. Hence, the establishing of HOSPITALS for the special treatment of inebriety, in which such conditions are recognized becomes a positive need of the age.

(American Association 1893, p.v.)

The American Association first published its journal, the ***Quarterly Journal of Inebriety,*** **in 1877.**

As for the transatlantic connections, Norman Kerr was an honorary member of the American Association and Dr. T. D. Crothers, secretary of that Association, was among those elected to honorary membership of the British Society at that inaugural luncheon meeting in 1884. Kerr and Crothers published in each other's journals (Crothers 1906).

In the early 1870s a delegation from the American Association gave evidence in London to a British Parliamentary committee which was considering inebriates legislation and the chairman of that committee, Dr Dalrymple, made a tour of inspection in the USA. Kerr had himself visited America on several occasions and in his earlier days he had been a ship's doctor on the transatlantic run. Kerr died in 1899 and it was Crothers who in October 1905 (Crothers 1906), honoured the memory of his colleague by delivering in London the first Norman Kerr Memorial Lecture which outlined Kerr's life and works. Crothers referred to the influence of Kerr's magnum opus, "Inebriety, its Etiology, Pathology, Treatment and Jurisprudence" (Kerr 1888). And he identified the inaugural address of 1884 as one of the "really great landmarks in the study of the subject".

One may infer that the American Association was in some ways a role model for its British counterpart. Jellinek (1960) in a brief note on this period of history asserted that the British journal "right from its beginnings, was on a much higher scientific level that its older American sister": in Jellinek's view it did not make such a cult of the disease (or illness) idea as its American contemporary. The whole issue of who contributed what over this period and the convergences and shades of difference between the American and British positions needs further elucidation (Lender 1979).

CONSEQUENCES

Kerr's inaugural address defined a specialist Anglo-American medical consensus on the disease nature of inebriety which had by the latter part of the 19th century emerged as an organizing idea which invited programmes of action very different from that of the other great nineteenth century evolution in this field, the temperance movement (Gusfield 1986). Here is a quotation from a contemporary of Kerr and Crothers, General William Booth (Booth 1890), the founder of the Salvation Army:

> Still the mighty torrent of alcohol, fed by ten thousand manufacturies, sweeps on, bearing with it, I have no hesitation in saying, the foulest, bloodiest tide that ever flowed from earth to eternity . We would to God that the temptation could be taken away from them, that every house licensed to send forth the black streams of bitter death were closed, and closed for ever. (Booth 1890, p. 186)

Despite the fact that Booth was willing on occasions to see drunkenness as a disease while at the same time Kerr, Crothers and many of their medical colleagues who favoured the disease formulation had strong links with the temperance movement, what stands out with great clarity is that by the latter part of the 19th century there were on both sides of the Atlantic models for understanding the drink problem between which informed opinion was being invited to choose (Edwards 1992). The availability of that choice is the true and conjoint heritage of the American Association and the British Society, and the value of that transcript of Kerr's address is that it provides us with a vivid, daguerreotype view of the then contemporary disease formulation. Building on our analysis of Kerr's inaugural talk and its AngloAmerican context, the question we will examine in this final section of our discussion is the consequences which flowed and still flow from the availability of a choice between models, a choice which must have been evident to Kerr's audience that afternoon and which has not gone away.

The bones of the argument around this consequences question will be as follows. It is a matter of identifying stages in a long historical process. In the first stage the disease model made an unsuccessful and short-lived entry on a scene where the temperance model was already strongly established, and choice was solved by the disease model going into eclipse and with the temperance model triumphant. In the second stage the temperance model was eclipsed, the disease model rode high and looked like providing a consensus around which all could rally. In the third stage, the present day, we again co-exist with choice. The models themselves have changed and developed over time, but there is still the inherent possibility of conflict between the formulations which view the drink problem as personally or alternatively as socially rooted, as affecting a few "diseased" people or as a wider social issue. Let's put a little evidential flesh on the bones of those contentions and then tackle our very last question, what next?

Stage one: the disease model is formulated, gains little ground, and goes into eclipse. One of the most persuasive kinds of evidence which could ever be deployed to support the contention that a model has gone into desuetude must surely be the death of the society which marches under its banner. The ***Quarterly Journal of Inebriety*** (by then published under another name) ceased publication in 1914 and the American Association itself faded into oblivion a few years later. The reasons for this outcome were several, but in the USA the dominant reason for the demise of the disease concept was the political ascendancy of the Temperance Movement leading to enactment in 1920 of Prohibition (Cherrington 1924-1930, Harrison 1971, Gusfield 1986, Levine 1992). Alcohol was deemed to be the cause of alcohol problems, pure and simple.

The parallel story was somewhat different in Britain. Although for some years after Kerr's death one can find luminaries of the Society for the Study of Inebriety paying homage to the disease concept and quoting from Kerr's inaugural address (Branthwaite 1908, Woodhead 1912), gradually both the disease idea and Kerr's name ceased to get a mention. By the time the Great War was finished the disease idea was probably as dead in Britain as in the USA. Prohibition was not part of the historical experience in the UK, but the introduction of stringent licensing controls together with changed social conditions brought alcohol consumption to an all time low (Wilson 1940). That the British Society continued to meet and publish its journal despite most sense of purpose having been lost speaks more to a national fondness for lost causes than anything else. The last Norman Kerr memorial lecture was given in 1943 and the endowment then ran out (Berridge 1990).

Stage two: The disease concept re-emerges as the new consensus. The story of the re-emergence of the disease concept in America from the 1940s onward has been well-chronicled and need not be repeated here in detail (Keller 1985, Roizen 1991). Suffice it to say that the conjoint influences of Alcoholics Anonymous, the Yale School, the National Council on Alcoholism and Jellinek's prestigious 1960 "Disease Concept of Alcoholism", made the disease formulation in post-war America the organizing idea for the new alcoholism movement (Levine 1978, 1984). A postulate had become a received truth. At the same time as the disease

concept won wide acceptance there was consensual rejection of the idea that alcohol was the problem. Alcohol was seen as having little to do with alcoholism.

Stage three: the consensus falls apart. At this point in our account of a complex history, the relative influence of different national ideologies and experiences becomes important to understanding what happened. The post-war rediscovery of the disease concept was very strongly led by America and can be seen as in part a reaction to the searing national experience with Prohibition. This American disease formulation was internationally influential, but did not swamp certain other national traditions. Thus in 1964 Ledermann, a French statistician, published data showing fluctuations in liver cirrhosis death rate in Paris and pointing up the steep dip in cirrhosis deaths which occurred when alcohol was rationed during the Second World War (Ledermann 1956, 1964); those data alone made it difficult to accept the view that alcohol and "alcoholism" were unrelated. Canadian work based on temporal and geographical comparisons confirmed the strong positive correlation between per capita consumption and cirrhosis death rate (Schmidt 1977). In 1975 what was essentially a joint Scandinavian and Canadian working group met under the leadership of Kettil Brunn, a Finnish researcher, and reviewed the evidence for the relationship between alcohol and alcohol problems and offered a strong conclusion (Bruun *et al.,* 1975):

> Changes in the overall consumption of alcoholic beverages have a bearing on the health of the people in any society. Alcohol control measures can be used to limit consumption: thus control of alcohol availability becomes a public health issue. (Bruun *et al.,* 1975, p. 12)

In 1994 a funkier review volume was published with a WHO connection (Edwards *et al.,* 1994), this time under the title "Alcohol Policy and the Public Good", and now with major US involvement as well as wider international representation. Among the conclusions offered was the following:

> We believe that the title of this book is well chosen. Policy to deal with the multifarious consequences stemming from alcohol cannot usefully be couched in terms just of 'excessive drinking' or 'right-hand end of the curve' policies disarticulated from the whole society, nor in terms just of 'alcohol problem policies', or 'How are we to deal with alcoholics?'. The requisite public policies are, in the round, alcohol policies. (Edwards *et al.,* 1994, p.212)

No wonder that in the light of the 1976 statement one could find David Pittman (1991), a respected contributor at several levels to the post-war American alcoholism movement, reflecting as follows:

> I think one of the tragic developments of the 1980s is the kind of schism which has developed in the alcoholism field. Many organizations, founded to help the alcoholic and his or her family, were organized on the assumption that they would take no position, either positive or negative, toward the sale or restriction on the sale of alcohol products. The type of alcohol policy neutrality from the 1940s through the 1970s set the stage for progressive developments in research, treatment, and education. The consensus has become unravelled in terms of the new 'public health model towards alcohol control'. (Pittman 1991, p.130)

And there can be no doubt that Pittman is right, the consensus has become unravelled. In the eye of history we can see that we are back to 1884, to a choice of competing models, and probably to an era of intellectual instability.

Stage four: finding a new way through. Though sharing Pittman's belief as to the fact that a change point has been reached and sensitive to his concern over the inevitable pains in any change, rather than going along with his sense of grief at the breakdown in the old consensus, some of us would perhaps want to argue that we are now necessarily and very probably faced with the challenge of building a new consensus more congruent with the established facts and more likely to provide us with apt research agendas and effective policy solutions, Change should be welcomed not feared, and if Thomas Kuhn is to be heeded, turmoil is the necessary prelude to paradigm shift (Kuhn 1970).

Here in the light of history and with due and grateful acknowledgement of Norman Kerr, T.D. Crothers and the long-standing American connection, let's make a proposal as to what may be the way constructively to handle the unravelling of what was in retrospect inevitably no more than a temporary consensus (as will be any new consensus that serves our own time). We need to find a way to escape from the "ding-dong", to-and-fro competition between models which have respectively seen the alcohol problem as individually rooted brain disease or alternatively as a socially determined consequence of alcohol's availability. An informed reading of the present state of scientific knowledge (Gordis 1991) must surely see such polarity as false antithesis, as absurd. One tradition to be integrated into a new synthesis must be the person-based view of the problem, and that embraces but is not co-terminus with an inebriety (Kerr 1884) disease (Jellinek 1960) alcoholism or dependence view (American Psychiatric Association 1994). The second tradition to be taken within the new synthesis is the population view which conceives of the drinking population as an organism to be understood in its own right (Skog 1985). That latter view is led by the belief that the individual's drinking is influenced by the social, cultural, economic and drinking context within which the drinker has his or her being; drinking has a great deal to do with drinking problems.

Integration of these two traditions should not mean two separate and incompatible models awkwardly bonded together and waiting to fall apan, but a true and mutually beneficial sharing of ideas and joint and practical exploration of the consequences which will flow from such sharing. Let's go back briefly to Kerr and see what that kind of synthesis might mean. You will remember that he postulated that one cause of inebriety was "The habit of drinking long continued". That is a phrase which carries a tangible invitation to conjoint modelbuilding. What is the influence of alcohol availability and social and cultural influence on intensity, duration and pattern of drinking, and what is likely to be the follow-through impact of these factors on the prevalence and incidence of the "brain-disease" of inebriety (Midanik 1995)? Price elasticities (Caulking and Reuter 1996) and neuro-transmitter systems (White 1996) at the end of the day inhabit one world. Dependence is a disturbance in a very complex system (Edwards *et al..,* 1981).

If we do not build consensus but allow our models to fall about in faction fighting, harm will be done. History by now shows a long period of cyclic triumph and rejection of competing models, with triumph each time wiping out much else which had usefully been learned. The record all too often shows people shutting out from consideration half of the evidence. Norman Kerr was neither the beginning nor the end and his consensus unravelled. But at the very least we may see him as pointing up the importance of history.

REFERENCES

American Association for the Study and Cure of Inebriety. The Disease of Inebriety from Alcohol. Opium and other Narcotic Drugs. its Etiology. Pathology. Treatment and Medico-Legal Relations. Bristol: John Wright, 1893.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, D.C.: American Psychiatric Association, 1994.

Berridge, V. (1990) The Society for the Study of Addiction 1884-1988. Brit J Addict 85, Number 8 (Special Issue), pp.983-1094.

Booth, W. [General] In Darkest England and the Way Out. London: Headquarters of the Salvation Army, 1890.

Branthwaite, R.W. (1908) Inebriety: its causation and control. The Second Norman Kerr Memorial Lecture. Brit J Inebriety 5, 105-128.

Brnun K., Edwards G., Lumio M., Maikela K., Pan L. and Popham R.E. *et al.* Alcohol Control Policies in the Public Health Perspective. Helsinki: Finnish Foundation for Alcohol Studies, 1975.

Caulkins, J. and Reuter, P. (1996) The meaning and utility of drug prices. Addict 91, 1261-1264.

Cherrington, E.H., ed. Standard Encyclopedia of the Alcohol Problem (6 volumes). Westeville, Ohio: American Issue Press, 1924-1930.

Crothers, T.D. (1906) The Norman Kerr Memorial Lecture. Brit J Inebriety 3, 105-126.

Edwards, G., Arif A. and Hodgson, R. (1981) Nomenclature and classification of drug and alcohol related problems: a WHO Memorandum. Bull of the World Health Organization 59, 225-242.

Edwards, G. Problems and dependence: the history of two dimensions. In: Lader M., Edwards G. and Drummond D.C., eds. The Nature of Alcohol and Drug Related Problems. Society for the Study of Addiction Monograph No.2. Oxford: Oxford University Press, 1992.

Edwards G., Anderson P., Babor T.F., Cassell S., Ferrence R. and Giesbrecht N. *et al.* Alcohol Policy and the Public Good. Oxford: Oxford University Press, 1994.

Gordis, E. (1991) From science to social policy: an uncertain road. J Stud Alc 62, 101-109.

Gusfield, J.R. Symbolic Crusade: status Politics and the American Temperance Movement (2nd ed.) Urbana, III.: University of Illinois Press, 1986.

Harrison, B. Drink and the Victorians. Pittsburgh, PA.: University of Pittsburgh Press.

Hirsh, J. (1949) Enlightened 18th century views of the alcohol problem. Journal of the History of Medicine 4, 230-236.

Jaffe, J.H. Drug addiction and drug abuse. In: Goodman L. and Gilman A., eds. The Pharmacological Basis of Therapeutics. New York: Macmillan, 1965, pp.247-284.

Jaffe, J.H. (1987) Footnotes in the evolution of the American national response: some little known aspects of the first American Strategy for Drug Abuse and Drug Traffic Prevention. Brit J Addict 82, 587-600.

Jaffe, J.H. Science, Policy, Happenstance. The Nathan B. Eddy Lecture. In: Harris L.S., ed. Problems of Drug Dependence 1994. NIDA Research Monograph 152, 1995, pp. 18-32.

Jellinek, E.M. The Disease Concept of Alcoholism. New Brunswick, N.J., Hillhouse, 1960.

Keller, M. (1985) Conversation with Mark Keller. Journal Interview 8. Brit J Addict 80, 5-9.

Kerr, N. (1884) President's Inaugural Address. Proceedings of the Society for the Study and Cure of Inebriety 1, 2-16.

Kerr, N. Inebriety, its Etiology. Pathology. Treatment and Jurisnrudence. 2nd ed. London: H.K. Lewis, 1889.

Kuhn, T.S. The Structure of Scientific Revolution. 2nd edit. Chicago, III.: University of Chicago Press, 1970.

Ledermann, S. Alcohol, Alcoholisme, Alcoholisation, Vol.1. Paris: Presses Universitaires de France, 1956.

Ledermann, S. Alcohol, Alcoholisme, Alcoholisation, Vo1.2. Paris: Presses Universitaires de France, 1964.

Lender, M.E. (1979) Jellinek's typology of alcoholism: some historical antecedents. Quart J Stud Alc 46, 361 -375.

Levine, H.G. (1978) The discovery of addiction: changing conceptions of habitual drunkenness in America. J Stud Alc 39, 143-174.

Levine, H.G. (1984) The alcohol problem in America: from temperance to alcoholism. Brit J Addict 79, 109-119.

Levine, H.G. (1992) Temperance cultures: concern about alcohol problems in Nordic and English speaking cultures. In: Lader M., Edwards G. and Drummond D.C., eds. The Nature of Alcohol and Drug Related Problems. Society for the Study of Addiction Monograph No.2. Oxford: Oxford University Press, 1992, Chapter 2, pp.15-36.

Midanik, L.T. Alcohol consumption and social consequences, dependence, and positive benefits in general population surveys. In: Holder, H.D. and Edwards, G., eds. Alcohol and Public Policy: Evidence and Isues. Oxford: Oxford University Press, Chapter 3, pp.62-81.

Pittman, D.J. Interview with David I. Pittman. In: Edwards G., ed. Addictions: Personal Influences and Scientific Movements. New Brunswick, N.J.: Transaction Publishers, 1991, Chapter 8, pp.105-142.

Porter, R (1985) The drinking man's disease: the "pre-history" of alcoholis,m in Georgian Britain. Brit J Addict 80, 385-396.

Roizen, R. The American Discovery of Alcoholsim 1933-1939. Dissertation for degree of Doctor of Philosophy in Sociology. Berkeley: University of California, 1991.

Rush, B. An Enquiry into the Effects of Spirituous Liquors on the Human Body. Boston: Thomas and Andrews, 1790.

Schmidt, W. Cirrhosis and alcohol consumption: an epidemiological perspective. In: Edwards G. and Grant M., eds. Alcoholism: New Knowledge and New Responses. London: Croom Helm, 1977, Chapter 1, pp.15-47.

Skog, O-J (1985) The collectivity of drinking cultures. A theory of the distribution of alcohol consumption. Brit J Addict 80, 83-99.

Trotter, T. An Essay, Medical, Philosophical and Chemical. on Drunkenness and its Effects on the Human Body. London: Longman, Hurst, Rees and Orme, 1804.

White, N.M. (1996) Addictive drugs as reinforcers: multiple partial actions on memory systems. Addict 91, 921-950.

Wilson, G.B. Alcohol and the Nation. London: Nicholson and Watson, 1940.

Woodhead, G.S. (1912) The action of alcohol on body temperature and the heart. The Fourth Norman Kerr Memorial Lecture. Brit J Inebriety 9, 109-137.

USING MOLECULAR BIOLOGICAL TOOLS TO EXPLORE BEHAVIOR

L. Erinoff and L. Gold

Behavioral research on drug abuse can be enhanced by the incorporation of molecular biological tools (antisense, knockouts, transgenics) into experimental strategies. Speakers addressed the strengths and weaknesses of the technique(s) they use.

Antisense Oligonucleotide "Knockdown" Strategies in Neuropharmacology

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Oligonucleotides that bind to single or double stranded nucleic acids provide an opportunity to rationally design true isotypically selective pharmacological agents and should allow the testing of many types of hypotheses in biomedicine. This presentation focuses on their use as neuropharmacological tools and the technological issues surrounding their direct application to the mammalian brain. Typically, efficacious oligonucleotides are identified in vitro and prior to in vivo studies. The use of stringent mismatched control sequences is essential. Some of the major advantages of antisense compared to the gene knockout are: the reversibility of the effect, applicability to any stage of development, ability to study the product of a cloned gene from any species, range of phenotypes that can be created, relatively low cost, and potential therapeutic use. The strengths of the knockout approach include: the complete absence of the gene product, specificity, and lack of variation between animals. Antisense oligonucleotides are perhaps especially useful for receptor research where a conventional antagonist is not available or shows limited selectivity. For drug discovery research, the knockdown approach is of value for target validation and identification.

Behavioral Studies of Monoamine Receptor Knockout Mice: Phenotypic and Pharmacological Differences

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The creation of gene knockout animals in which a particular neurotransmitter-relevant gene has been deleted may facilitate the identification of functional roles for particular receptors and even provide models for disease states. Schizophrenic and schizotypal subjects exhibit deficits in both the habituation and prepulse inhibition (PPI) of acoustic and tactile startle, providing operational measures of the sensorimotor gating deficits that may contribute to cognitive disorganization. In rats, developmental and pharmacological manipulations affecting central dopaminergic, serotonergic, and/or glutamatergic systems have been used to induce similar deficits in sensorimotor gating. The present studies have begun to extend this approach to mice in order to capitalize upon the availability of genetically modified animals. Mice were subjected to 120 dB acoustic pulses, some of which were preceded (100 msec) by prepulse stimuli that ranged from 2 to 16 dB above the 65 dB background. As in rats, the amount of PPI was decreased significantly in mice treated with amphetamine, apomorphine, phencyclidine, MDMA, or RU 24969. The 5-HT-1A agonist 8-OHDPAT increased PPI in mice. Mice lacking the 5-HT-1B receptor (provided by R. Hen) exhibited abnormally high levels of PPI in the absence of drug. As expected from the relative receptor specificities of RU 24969 and 8-OHDPAT, the PPI-disruptive effects of RU 24969 were absent in the 5-HT-1B knockout mice, while the PPI-increasing effects of 8-OHDPAT were maintained. By contrast, studies of mice lacking the dopamine D4 receptor (provided by M. Low and D. Grandy) have revealed normal PPI in the knockout animals. Furthermore, the effects of amphetamine and apomorphine on PPI appeared to be unaltered in the D4-deficient mice. These studies demonstrate the

pharmacological sensitivity of the PPI paradigm for studies in wild-type and genetically modified mice and confirm that the knockout procedure can selectively modify the responses of animals to appropriate agonists. Supported by NARSAD and DA09862.

Challenge Strategy for Characterizing Knockout Mice

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Pharmacological evidence implicates CRF and CCK-B CNS receptors in a wide range of physiological and behavioral processes, most prominently in how individuals react to and cope with a range of stressful, aversive life events. A strategy was developed to characterize behavioral patterns in those mutant mice who lacked the gene for CRF or CCK-B in comparison to their heterogeneous wild-type counterparts in a stepwise progression from situations that involved very brief stresses to more intense prolonged ones. In the initial stage, mice were exposed to novelty stress in an open-field where their thigmotaxis response as well as their exploration of exposed brightly lit areas could be measured by an image analysis system. After the mice had habituated as indicated by an exponential decline in exploratory behavior, dishabituation probes were inserted. Behavior in open, unwalled arms of a plus-maze served as a further index of exploratory behavior that is sensitive to pharmacological manipulation of CRF and CCK-B receptors. In a learning situation, mice were assessed for their rate of acquisition of food-reinforced responding and their response to extinction ("frustrative non-reward") as well as the stress of food restriction. Reflexive responses to startling and painful stimuli reflect spinally and supra-spinally mediated processes that are gated by descending information. In the final stage, the mice were challenged as "intruders" with social provocations in the form of threats and attacks by an aggressive resident. The data suggest important redundant and compensatory mechanisms for survival behavior which is only moderately affected by a single gene.

Integration of Transgenic Mouse Models and Behavioral Analysis

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Intravenous drug injection, as well as lifestyles that promote high risk behaviors, renders the drug abusing population particularly vulnerable to the spread of HIV infection. A critical hypothesis for this vulnerability is the influence of drugs of abuse on disease progression. Direct neurotoxic effects of drugs, in addition to their effects on immunocompetence, may contribute to an enhancement of the neurobehavioral dysfunction associated with HIV infection, or accelerate its onset. Candidate mediators of neuropathogenesis include virus-derived (gp120) and host-derived (IL6, IFNa) factors. One experimental model involves the transgenic expression of gp120, the HIV coat protein, which has been shown to be toxic *in vitro* and to produce retardation of developmental milestones and spatial learning impairments *in vivo*. Two additional models involve the transgenic expression of the cytokines, IL6 and IFNa. IL6 has been shown to have a direct pathogenic role in various inflammatory, infectious, and neurodegenerative CNS diseases. The interferons are antiviral host defense molecules, and exogenous administration of IFN mimics many of the CNS symptoms of HIV infection. These transgenic mouse models exhibit unique neuropathological changes that replicate specific aspects of clinicopathology seen in neuroAIDS. Characterization of behavioral phenotypes in these transgenic mice is ongoing. A powerful method for perturbing behavior and exaggerating potential differences between experimental groups involves the use of pharmacologic agents with known neurobehavioral actions to probe potential underlying neurochemical differences between groups and to reveal dysfunction of specific neurotransmitter systems. Transgenic mice can be trained to self-administer drugs intravenously and then tested for neurobehavioral function and responsiveness to acute drug probes in tasks assessing other behaviors such as learning, motor activity, and analgesia. Behavioral studies can be complemented by studies of molecular and

cellular neuropathology, as well as peripheral immune parameters. Such an approach integrates analysis of drug effects on CNS and immune function, as relates to components of HIV disease progression, across several levels of investigation. Converging results should go far in identifying critical viral- and host-derived factors associated with increased susceptibility to the pathobiological effects of drugs of abuse and consequent synergistic neurotoxicity. Equally important, these studies will help to determine the nature of viral neuropathogenesis to specific brain systems relevant to drug reward, which may have significant clinical outcomes in terms of altered neurobehavioral and pharmacological sensitivity to drugs of abuse in HIV infected individuals.

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DRUGS OF ABUSE AND THE IMMUNE SYSTEM

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Opiates, Opiate Receptors and Signal Transduction in Lymphoid Tissue

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Endogenous opioid peptides secreted from neural, endocrine and immune tissues directly impact immune function. Opiate alkyloids such as morphine are also immunomodulatory. Both pharmacological and molecular approaches indicate that lymphocytes obtained from human, simian and murine tissues express opioid receptors that are similar to those present in neural tissues. Opiate modulation of both humoral and cell-mediated immunity is due in part to effects on T lymphocytes. Delta opioid receptor (DOR) agonists have been shown to modulate crucial events involved in T-cell activation including (i) the proliferative response to crosslinking the CD3 complex associated with the T-cell antigen receptor (TCR), and (ii) the production on interleukin-2 (IL-2) which is involved in progression from G1 to S phase of the cell cycle (Shahabi and Sharp 1995). To understand DOR-mediated signal transduction in T-cells, the cDNA encoding this receptor was. stably expressed in Jurkat cells, a human T-cell line (Sharp *et al.* 1996). This model was used to determine whether intracellular calcium and cAMP mediate signaling through the neuronal DOR expressed by T-cells. DOR agonists, deltorphin and [D-Ala^2,D-Leu^5]-enkephalin (DADLE), elevated intracellular calcium ([Ca^{2+}],) at concentrations from 10^{-11}- 10^{-7} M (Sharp *et al.* 1996); both agonists dose-dependently increased [Ca^{2+}], from 60 mM to peak concentrations of 400 nM within 30 sec (ED_{50} of approximately 5 x 10^{-9} M). Naltrindole, a selective DOR antagonist, abolished the increase in $[Ca^{2+}]_i$, as did pertussis toxin. To assess the role of extracellular calcium, cells were pretreated with EGTA which reduced the initial deltorphin-induced elevation of [Ca^{2+}], by more than 50% and eliminated the second phase of calcium mobilization. Forskolin-stimulated cAMP production was reduced 70% by DADLE (IC_{50} of approximately 10^{-11} M) and pertussis toxin also inhibited this. Thus, the DOR expressed by a transfected Jurkat T cell line is positively coupled to pathways leading to calcium mobilization and negatively coupled to adenylate cyclase. These studies identify 2 pertussis toxin-sensitive G-protein mediated signaling pathways through which DOR agonists regulate the levels of intracellular messengers that modulate T-cell activation. Endogenous opioid peptides, such as β-endorphin, have been reported to modulate T cell function through opioid and non-opioid receptors (Shahabi *et al.* 1990). Therefore, investigations were undertaken to determine whether β-endorphin affects the mobilization of [Ca^{2+}], by murine splenic T cells. Since opioid peptides modulate activation induced by mitogens or anti-CD3, the effects of β-endorphin, alone, and in conjunction with concanavalin A (Con A) were studied. Con A was selected because of its efficacy in inducing calcium mobilization by both $CD4^+$ and $CD8^+$ T-cells. The [Ca^{2+}], of T cell enriched splenocytes was measured, and by gating on the T cell marker, Thy-l, a 95%-pure population of T cells was identified for study (Shahabi *et al.* 1996). Cells preincubated with β-endorphin showed significantly enhanced [Ca^{2+}], responses to the mitogen, Con A. This was detectable with concentrations of β-endorphin as low as 10^{-13} M; maximal enhancement required 10^{-10}-10^{-9} M doses. The efficacy of β-endorphin was dependent on the duration of pre-treatment. β-Endorphin amplified the Con A-induced increase in $[Ca^{2+}]_i$ by reducing the lag time for the response to Con A and by increasing the mean [Ca^{2+}], of the cells. N-Ac-β-endorphin, which shows minimal potency at neuronal opiate receptors, was unable to substitute for β-endorphin. Naltrindole, a highly selective DOR antagonist, inhibited the action of β-endorphin, whereas a selective mu opiate receptor antagonist was ineffective. Although less potent than β-endorphin, DADLE also significantly enhanced [Ca^{2+}], responses. In summary, concentrations of β-endorphin, within the physiological range found in the systemic circulation, modulate the increase in T cell $[Ca^{2+}]_i$ induced by Con A. Both the efficacy of DADLE alone and the antagonism of β-endorphin by naltrindole suggest that a delta-type opiate receptor may mediate these effects.

Fluorescent Labeling of the Kappa Opioid Receptor on Cells of the Immune System

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Recent studies have shown the labeling of κ opioid receptors on the R1EGO thymoma cell line by indirect immunofluorescence and flow cytometric analysis (Lawrence *et al.* 1995). The present study employed a fluorescein-labeled acrylacetamide (FITCC-AA), a κ-selective opioid, in conjunction with biotin-conjugated, anti-fluorescein IgG and extravidin-R-phycoerythrin, along with double-labeling using antibodies against specific immune cell surface markers to determine which subpopulation of lymphocytes express the κ opioid receptor. Thymocytes, isolated from 6-8 week old, male C57BL/6ByJ mice, were incubated with FITC-AA followed by the phycoerythrin amplification procedure demonstrating labeling of the κ opioid receptor. This labeling was

blocked 55 ± 4% by excess nor-binaltorphimine (nor-BNI), a κ- -selective antagonist, but was not blocked by selective δ or μ opioids. This κ opioid receptor positive cell population consisted of 58± 2% of all gated thymocytes. Phenotypic characterization determined that not only were 64 ± 3% of the gated thymocytes $CD4^+$/κ opioid receptor positive, but 60 ± 1% of all thymocytes were $CD8^+$/κ opioid receptor positive. Two distinct subpopulations of $CD3^+$ thymocytes, consisting of immature and mature cells, also displayed labeling for theopioid receptor. Double-labeling of thymocytes with anti-CD4 and anti-CD8 antibodies demonstrated 82 ±0.5% of these cells were of the double-positive phenotype. Therefore, these findings demonstrate that the thymocytes were predominantly of the immature $CD4^+/CD8^+$ phenotype, and the majority of these cells express the κ opioid receptor. Collectively, these findings not only establish the presence of the κ opioid receptor on immune cells, but further indicate that this technique allows for the identification of distinct lymphocyte subpopulations which express the receptor. (Supported by USPHS grants DA04355 and DA 09676)

Induction of IL-2 Receptor α Gene by Δ^9-tetrahydrocannabinol Is Mediated by NF-κB and CB1

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The cannabinoid, Δ^9-tetrahydrocannabinol, increases expression of IL-2 receptor α and β proteins and mRNAs, but decreases the level of the γ message in natural killer cells (Zhu *et al.* 1995). The drug increases the β chain message stability rather than affecting rate of transcription. In the present study, we examined the mechanism responsible for the drug-induced increase in the IL-2 receptor α chain message. Nuclear run-on and mRNA stability studies show Δ^9-tetrahydrocannabinol increases the transcriptional level of IL-2 receptor α but has no effect on mRNA stability. Because expression of this gene is regulated by nuclear factor κB (Leung and Nabel 1988), we tested the effect of drug treatment on the nuclear level of this protein using the electromobility shift assay. These studies show a drug-induced increase in nuclear factor κB activity. To link this increased activity with the increase in IL-2 receptor α message, antisense oligodeoxynucleotides were used to inhibit expression of the RelA component of nuclear factor κB. These studies show anti-RelA antisense eliminates the cannabinoid-induced upregulation of IL-2 receptor κ mRNA. Furthermore, inhibition of the cannabinoid receptor type 1 with antisense oligomers also eliminates the drug effect on the IL-2 receptorα message. These results suggest that Δ^9-tetrahydrocannabinol treatment of NKB61A2 cells increases IL-2 receptor α gene transcription by increasing the nuclear level of nuclear factorκB through a mechanism involving cannabinoid receptor type 1. Finally, it is possible to speculate that marijuana abuse might augment AIDS development due to an increase in nuclear factor κB which is known to activate the HIV genome and increase retroviral replication (Pierce *et al.* 1988).

Effects of Opioids on Immune Function and Host Defense to Infection

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This lecture was a tutorial overview of the field to synthesize the work which supports the conclusion that opioids are immunomodulatory. The literature on the effects of morphine and other opioids on immune responses and susceptibility to infection was reviewed and data from our laboratories was presented to illustrate specific points. Three paradigms were presented: administration of drug *in vivo* with measurement of *in vivo* effects on immune and host defense responses; administration of drug *in vivo* with measurement of *in vitro* effects; and addition of drug *in vitro* to cells of the immune system. The specific papers cited have been collected in a recent review (Eisenstein *et al.* 1995). Morphine given *in vivo* to mice has been shown to inhibit serum antibody responses to tetanus toxoid (Eisenstein *et al.* 1990), sheep red blood cells, and trinitrophenyl-bovine serum albumin. Further, delayed type hypersensitivity, a measure of cellular immunity, has been shown to be inhibited in rats, mice, and pigs by morphine. In models of infection, morphine has been shown to sensitize mice to the yeast, *Candida albicans;* the protozoan, *Toxoplasma gondii;* the bacterium, *Listeria monocytogenes;* and to encephalomyocarditis virus and Friend Leukemia virus. Morphine also sensitized pigs to bacterial pneumonia in animals infected with swine herpesvirus, and monkeys to Simian Immunodeficiency Virus. If morphine was given *in vivo* and cells from treated animals were placed in culture, suppressive effects were seen in a number of different assays of immune function. Mouse spleen cells exhibited depressed capacity to mount *in vitro* antibody responses to sheep red blood cells (Bussiere *et al.* 1992) and mouse bone marrow precursors were less able to develop into macrophages *in vitro.* Mitogen responses of mouse spleen cells to B- and T-cell mitogens were suppressed, as were responses of rat peripheral blood mononuclear cells to a T-cell mitogen. The capacity of human T-cells taken from addicts to rosette with sheep red blood cells was diminished. Natural killer

cell activity in rat and mouse spleens and in peripheral blood of rhesus monkeys was depressed. Phagocytic capacity of mouse peritoneal cells to ingest yeast was also depressed. An important question in the field is whether the effects of morphine given *in vivo* are directly on cells of the immune system or whether they are

mediated, for example, by products of the sympathetic nervous system or the HPA axis. A definitive approach to this question is the design of *in vitro* experiments where the drug is added to immune cells in culture, thus bypassing other physiologic systems of the host. Using the *in vitro* approach, human T-cells have been shown by three different groups to be inhibited in their ability to rosette with sheep red blood cells. Mouse (Taub *et al.* 1991) and rat spleen cells have been shown to be inhibited in their capacity to mount an *in vitro* response to sheep red blood cells. The kappa agonist, U50,488H, has also been shown to be active in this assay by two different laboratories. Strain differences among mice were noted in regard to *in vitro* activity of morphine and U50,488H (Eisenstein *et al.* 1995). As formation of antibody to sheep red blood cells requires B-cells, T-cells, and macrophages, the nature of the target cell cannot be' determined without further experimentation. Cell fractionation studies have shown that both T-cells and macrophages are inhibited by U50,488H, and an effect on B-cells could not be ruled out. The majority of *in vitro* studies have been carried out on phagocytic cells. Chemotaxis of human peripheral blood mononuclear cells and polymorphonuclear cells was inhibited by morphine. Mouse peritoneal macrophage phagocytosis of sheep red blood cells and yeasts was inhibited. Further, the respiratory burst of human peripheral blood mononuclear cells was depressed, as was their capacity to release tumor necrosis factor and interferon-y. U50,488H inhibited release of interleukin-1 and tumor necrosis factor from a mouse macrophage cell line and from primary murine peritoneal macrophages. These results show a substantial body of literature in which morphine was demonstrated to have a direct action on cells of the immune system. The literature shows that morphine, both *in vivo* and *in vitro,* is immunosuppressive. Further, while some of the *in vivo* effects may be mediated, direct effects on cells of the immune system, particularly professional phagocytes, can be demonstrated. Therefore, direct effects on immune cells may result in alteration of many of the parameters of immune function which have been observed.

Effect of Morphine on *Mycobacterium bovis* Infection of Porcine Alveolar Macrophages

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Mycobacterial infection has become one of the most common causes of morbidity and mortality for individuals who use morphine for post-operative pain control, during cancer therapy, as IVDU, and in persons infected with HIV (Friedman *et al.* 1996). Mycobacteria survive and replicate within the macrophages of these patients (Ellner and Wallis 1989), with the alveolar macrophage (AM) being the most critical cell for the outcome of infection. We have initiated studies to analyze the effect of morphine, administered *in vitro* and *in vivo,* on the susceptibility of porcine *AM* to *Mycobacterium bovis* infection. AM were collected by sterile lung lavage from 8-12 week old, conventional pigs and placed in media containing morphine sulfate between 10^{-6} M and 10^{-20} M. M. bovis was added at a 10:1 ratio to AM at 0, 2, and 24 hours after initiation of morphine treatment. Cell-associated bacilli were quantitated by auramine-rhodamine staining at 18 hours p.i. by fluorescence microscopy. This timepoint was chosen to maximize the amount of uptake before the occurrence of a replication cycle by the mycobacteria. Under the *in vitro* morphine conditions we tested, susceptibility of AM to M. *bovis* infection was not altered (n = 12). Using a model of chronic morphine administration (Risdahl *et al.* 1992), AM from pigs administered morphine *in vivo* were infected with M. *bovis* as described for the *in vitro* morphine experiments. AM from the chronic morphine pigs were significantly less susceptible to infection by M. *bovis* ($p > 0.003$, n = 17), which is consistent with a defect in phagocytosis by AM as observed by others (reviewed in Eisenstein *et al.* 1995). We also measured replication of M. *bovis* from the morphine-treated AM by lysing the cells at 0, 4 and 7 days post-infection and plating the lysates to determine colony forming units (cfu). In morphine-treated AM, we observed a nearly twofold increase in replication at day 4 ($p < 0.01$, n = 7), which is no longer statistically significant at day 7. In summary, under the conditions described, we have not observed an effect of *in vitro* morphine treatment on the susceptibility of AM to mycobacterial infection. However, we have seen a significant reduction in the uptake of mycobacteria by AM from morphine-treated pigs, and an increase in the replication of M. *bovis* in these cells. Future studies will focus on the mechanisms by which morphine' may be altering susceptibility, and on an infection paradigm of *in vivo* morphine, *in vivo* mycobacteria infection. (Supported by NIDA grant DA07239)

Effects of Morphine or Methadone Treatment on Immune Responses in Recombinant gp120-treated Mice

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In the present study, the immune effects of morphine or methadone administration were compared in a murine model in response to an HIV antigen, gp120. Female C3HeB/FeJ mice were either implanted with a 75-mg morphine pellet (MOR-pelleted) on Day 1, injected SC daily with 50 mg/kg of morphine (MOR-injected) or 20 mg/kg of methadone (METH-injected) and assessed for antibody response and delayed-type hypersensitivity (DTH) response to rgp120. All mice were vaccinated SC with 200 µl of 75 µg/ml rgp120 with QS-21 adjuvant on Days 1 and 8. Antibody titers to rgp120 were measured on Day 14 by an ELISA; DTH responses were measured by footpad swelling 24 hours after SC challenge with rgp120 on Day 14. We have shown previously that morphine pellet implantation suppresses both antibody and DTH response to rgp120 (Virsik and Bussiere 1995). The 50 mg/kg/day dose of morphine has been shown previously to suppress immune responses (Carr *et al.* 1995), while the 20 mg/kg dose of methadone had no effect on antibody responses after 5 days (LeVier *et al.* 1995). In this study, animals implanted with a morphine pellet had significantly suppressed antibody and DTH responses to rgp120. However, there was no difference in antibody or DTH response to rgp120 in the MOR-injected or METH-injected mice compared to controls (receiving daily SC injections of saline). Serum levels of morphine or methadone were assessed by radioimmunoassay. It appears that the daily doses of morphine and methadone may not have maintained sufficient serum levels to induce immunosuppression as seen with the continuous serum exposure in morphine-pelleted animals. Therefore, we tried a dose escalation method to see if we could maintain chronic exposure and more closely mimic the serum levels seen with morphine pellet implantation. Animals were injected SC daily with a dose escalation of morphine (MOR-injected [DE]; 50 mg/kg, 75 mg/kg, and 100 mg/kg increased every five days) or methadone (METH-injected [DE]; 20 mg/kg, 35 mg/kg, and 40 mg/kg increased every five days) starting on Day -2. Antibody responses were suppressed approximately 40-45% in both MOR-injected (DE) and METH-injected (DE) mice, although this difference was not statistically significant. However, DTH responses were significantly suppressed in both MOR-injected (DE) and METH-injected (DE) mice. Chronic administration of morphine via pellet implantation suppressed humoral and cell-mediated immune responses, however intermittent, escalating exposure via daily SC injections to morphine or methadone suppressed only cell-mediated immune responses. There appears to be no difference in the immune responses of methadone- or morphine-injected mice in this model.

Modulation of Immune Function *In vivo* by a Non-peptidic δ Receptor-selective Opioid Agonist

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Opioids have a variety of effects on immune system function *in vivo* and *in vitro*. We have examined indirect opioid/immune interactions *in vivo* by studying the neuroanatomical, pharmacological, and structure/activity relationships of opioids and immune function. Injection of opioid receptor subtype-selective agonists and antagonists centrally has allowed the delineation of CNS opioid receptor subtypes regulating immune function. Our studies indicate that certain CNS regions and µ opioid receptor-selective agonists mediate opioid-induced immunosuppression of natural killer (NK) cell activity (Weber and Pert 1989, Band *et al.* 1992). Central actions of δ and µ receptor-selective opioids have immunomodulatory effects that differ from µ actions (Band *et al.* 1992). Recently we have identified a non-peptidic δ receptor-selective opioid which is devoid of certain immunosuppressive properties induced by y-selective agonists. Whereas µ agonists induce suppression of splenic NK activity and T-cell proliferation in response to various doses of IL-2, R73 (antibody to CD3/TCR), or IL-2 + R73, ICV administration of δ agonist did not produce these effects. Similarly, thymic T-cells showed no functional changes. Also, flow cytometric analysis revealed no change in cell populations (CD3, CD4, CD8, NK) or in cell surface antigen density from either tissue compartment. Interestingly, certain non-peptidic δ-selective opioids have the ability to potentiate T-cell proliferation through direct interactions with putative leukocyte opioid receptors (Sanchez *et al.* this volume). These results suggest that this opioid agonist could be useful in clinical situations such as 1) the treatment of pain where suppression of NK cell activity is undesirable, *i.e.,* burn victims or cancer patients opting for adoptive immunotherapy or 2) where enhancement of immune function is desired, such as infectious disease, including AIDS. (Supported in part by NIH grant DA/A I08988) References furnished upon request of senior authors.

MARIJUANA USE: BASIC MECHANISMS, EPIDEMIOLOGY, NATURAL HISTORY, AND CLINICAL ISSUES

A. J. Budney,[1] D. B. Kandel,[2] D. R. Cherek[3] B. R. Martin,[4] R. S. Stephens,[s] C. R. Schuster[6]

University of Vermont,[1] Columbia University,[2] University of Texas-Houston,[3] Virginia Commonwealth University,[4] Virginia Polytechnic Institute and State University,[5] Wayne State University[6]

Although marijuana has been the most widely used illicit drug of abuse over the past 30 years, there has been relatively little scientific attention focused on marijuana's addictive potential or on clinical issues concerning abuse. The goal of this symposium was to provide a broad overview of recent research addressing marijuana as a drug of abuse. The participants provided experimental data from the basic laboratory to the clinic that addressed issues of dependence, motivational effects, epidemiology of dependence, and clinical management of marijuana use or abuse.

Dr. Martin began the symposium with a review of preclinical findings addressing the biological basis for the development of tolerance and dependence. In particular, he reviewed evidence that clearly demonstrates the existence of a functional endogenous cannabinoid system in the central nervous system. The characterization and localization of cannabinoid receptors in brain, the identification of second messenger systems that involve adenylyl cyclase and N-type calcium channels, the discovery of the endogenous ligand anandamide, and the most recent development of a specific cannabinoid antagonist have provided the basic tools for pursuing the mechanisms underlying the development of tolerance and dependence to cannabinoids. It has been well established that tolerance develops to all of the centrally mediated effects of cannabinoid following chronic treatment. Several laboratories have reported receptor down-regulation in animals tolerant to cannabinoids. Dr. Martin's laboratory also found down-regulation of cannabinoid receptors in the cerebellum with a concomitant increase in receptor mRNA levels in mice chronically exposed to CP 55,940, a potent cannabinoid analog. The unanswered question is the cause-effect relationship between alterations in receptor and mRNA levels. In addition, it is unknown whether comparable changes in mRNA occur in other brain areas that exhibit receptor down-regulation in the tolerant state.

The degree to which dependence occurs to cannabinoids has been controversial, in part because animal models of dependence have been lacking. The development of the specific cannabinoid antagonist, SR 141716A, afforded for the first time the possibility of precipitated withdrawal. In studies in which rats were chronically infused with 9-THC for four days (escalating doses of 2.5, 5.0, 10 and 20 mg/kg/day on each successive day) or mice were administered twice daily injections of 9-THC (10 mg/kg/injection, i.p.) for seven days, the animals exhibited profound withdrawal signs when challenged with the antagonist. The most prominent withdrawal signs were "wet-dog" shakes and facial rubbing in rats and paw-tremors in mice. The onset of effects occurred within ten minutes of the SR 141716A challenge and were evident an hour later. The development of this model demonstrates unequivocally that dependence develops to 9-THC and provides a means for exploring the mechanisms underlying biochemical adaptation that occurs in response to continual cannabinoid exposure.

Dr. Cherek presented experimental data that addressed the direct effects of marijuana smoking on human motivation. First, Dr. Cherek described an interesting laboratory developed by his group for the purpose of operationalizing the construct of motivation. The procedures used to measure motivation were based on a behavior analytic model; in this protocol, the index of motivation was sensitivity to changes in reinforcer magnitude.

Human subjects were given the opportunity lo earn points exchangeable for money either by pushing a button on a progressive-ratio schedule or by not responding and receiving points on a fixed-time schedule. During each experimental session, subjects began in the progressive-ratio schedule. Subjects had the option of switching to the fixed-time schedule by emitting ten responses on an appropriate button. Using these schedule contingencies, they examined the effects of smoking placebo or three potencies of marijuana cigarettes on the total number of responses, and response rate in the progressive ratio component as well as the number of points earned and time spent in the progressive-ratio and fixed-time components.

Marijuana smoking produced a reduction in responding in the progressive-ratio component and earlier escape to the fixed-time response independent point presentation. These effects were diminished by increasing the point value. These results are consistent with an interpretation of a "motivation-reduction" effect of marijuana. An interesting discussion concerning how these findings contrast with prior laboratory and clinical research followed the presentation.

Dr. Kandel then presented some new data on the epidemiology of marijuana dependence. She advanced the idea that progress in understanding the phenomenology of substance use and dependence will come from an integration of different research traditions in the epidemiology of drug behavior. In particular, such an integration will involve research on substance dependence, which emphasizes functional impairment to the neglect of patterns of use, and research on substance use in the general populalion, which usually ignores dependence or abuse criteria. Dr. Kandel described her ongoing work on marijuana use and last year dependence that bridges these two research traditions. Five issues were addressed: (1) periods of active marijuana use from adolescence to adulthood; (2) rates of last year marijuana dependence compared with dependence on alcohol, nicotine, and cocaine; (3) rates of last year marijuana dependence in different age, gender, and ethnic groups in the United States; (4) the relationship between intensity of marijuana use and dependence; and (5) aspects of marijuana consumption that account for gender and age specific differences in rates of marijuana dependence. The research was based on two samples: a longitudinal cohort followed for close to 20 years, the New York State Cohort, and three aggregated waves (1991-1993) of the National Household Survey on Drug Abuse (NHSDA). A proxy measure of DSM-IV last year marijuana dependence in the NHSDA was derived from self-reported symptoms of dependence, data on frequency and quantity of use, and drug-related problems experienced within the last 12 months.

Findings showed that marijuana use peaks at ages 19-23 among male and female marijuana users. Rates of last year dependence are much higher in adolescence than at any other age. Among adolescent users a somewhat higher proportion of females than males are dependent on marijuana although this difference is not statistically significant. Among adults, the rates are significantly higher among the male than the female users up to age 50. Both frequency and quantity of use are linearly associated with the probability of being dependent on marijuana. The associations vary significantly by age but not by gender. Adolescents become dependent at a lower threshold than adults; the differences diverge further as the intensity of use increases. In multivariate logistic analyses, both frequency and quantity of use retain a unique effect on marijuana, although frequency appears to be more important than quantity in predicting dependence when controlling for covariates.

These results provide insight into the process underlying the age and sex differentials observed in the prevalence of marijuana dependence. Adolescents may be more dependent than adults on marijuana because they experience symptoms of dependence at a lower threshold of use than adults. Adult females experience lower rates than adult males perhaps because they use at lower frequency and quantity levels than males. The implications of these findings for epidemiological study of drug abuse generated much discussion from the audience.

Dr. Budney presented data on clinical issues related to marijuana as a secondary drug of abuse. Estimates of the prevalence of marijuana use have ranged from 25% to 90% among cocaine and opiate abusers. His research seeks to provide scientilic information relevant to the question of how to most effectively address marijuana use in cocaine and opioid-dependent patients. Data were presented from five studies. Studies 1 and 2 examined relations between marijuana use and sociodemographic, psychosocial, and drug-use variables among cocaine- and opiate-dependent outpatients. Marijuana involvement was associated with reports of greater psychosocial impairment, health problems, risk-taking behavior and drug-use severity. These marijuana-associated problems did not appear to be a function of other sociodemographic or substance-use variables. Although many indicators of problem severity did not differ between marijuana-use groups, the types of impairment observed were consistent with findings from prior general population and clinical studies of marijuana users.

Study 3 examined patient reports of readiness to change their use of specific drugs of abuse. Two University of Rhode Island Change Assessments, one modified to assess stage of change regarding cocaine or opioid use and the other marijuana use, were administered to cocaine- and opioid-dependent outpatients who reported concurrent marijuana use. Significant differences were observed between primary drug and marijuana on all four stages of change for both patient groups, Precontemplation scores were higher for marijuana than cocaine or opioids; while, contemplation, action, and maintenance scores were lower for marijuana than for cocaine or opioids. These findings support the common clinical impression that many cocaine and opioid abusers who use

marijuana enter treatment at different levels of readiness for change regarding each of these drugs; moreover, many of these patients do not express interest in changing their marijuana use.

Studies 4 and 5 examined the effects of marijuana use on treatment outcome among cocaine- and opiate-dependent patients receiving outpatient behavioral or pharmacological treatments. No adverse relations were observed between marijuana use prior to or during treatment and any outcome measures (*i.e.,* drug abstinence or psychosocial functioning). These observations challenge the common assertion that drug-dependent patients must simultaneously cease use of all drugs of abuse to make progress in treatment. Alternative treatment strategies for addressing polydrug use were discussed. Dr. Budney's research raised questions regarding how to address marijuana use among cocaine- or opioid-dependent patients. The present data suggest that a flexible approach that discourages marijuana use but does not mandate abstinence may be a reasonable treatment strategy.

Dr. Stephens presented assessment and treatment outcome data from two clinical trials of adults seeking treatment for marijuana dependence. Both studies excluded persons with alcohol or other drug problems. Of particular note were the large number of individuals who sought treatment when marijuana-specific programs were publicized. The first study screened 385 individuals to arrive at a final sample of 212; while the second study screened 602 to obtain 291 for the study. Most subjects were white, educated and in their late 20's to early 30's. These users averaged over ten years of near-daily use, had made several serious quit attempts, and persisted in using despite social psychological and physical impairment consistent with cannabis dependence.

In the first study, participants were randomly assigned to a Relapse Prevention (RP) group or a Social Support (SS) group treatment. Each treatment consisted of ten, two-hour group sessions. The RP intervention emphasized a learning model of addiction, cognitive-behavioral coping skills training, and anticipation and planning for high risk situations for relapse. The SS condition relied on group social support for change. Although 63% of subjects in both treatments reported abstinence for at least the last two weeks of the treatment period, only 49%, 37%, 22%, 19%, and 14% of the sample remained continuously abstinent al the 1, 3, 6, 9, and 12 month posttreatment follow-ups, respectively. Mean days of marijuana use per month at the respective follow-ups were approximately 8, 10, 13, 14, and 14. These means reflect significant reductions from the pretreatment level of 27 days. When improvement was defined as at least a 50% reduction in days of use with no concurrent report of problems, 36% of the sample was improved during the final three months of the follow-up period. Data collected from collateral informants and urinalyses provided strong support for the validity of the self-reported use. Abstinence rates, days of marijuana use and reports of problems related to use did not differ between groups at any follow-up point.

In the second study, participants were assigned either to a longer RP group treatment (14 sessions), a two-session individual motivational interviewing intervention, or a four-month delayed treatment control. Although both active treatments showed superior outcomes at 16 months post-initiation of treatment, there were no significant differences between the active groups in abstinence rates, days of marijuana use, or report of problems related to use. Taken together, the results of both studies suggest that adults who are dependent solely on marijuana respond well to several types of interventions. Moreover, brief individual interventions may be as beneficial and more cost-effective than extended group counseling efforts, at least in the population reached in the present studies. Interestingly, the relapse rates among these marijuana abusers were comparable to rates observed in treatment populations of abusers of other drugs. These data indicate a continued need to develop more effective treatments for marijuana abusers.

Presenters and Titles

B.R. Martin	Status of the cannabinoid receptor during the development of tolerance and dependence
D.R. Cherek	Amotivational effects observed in humans after marijuana smoking under laboratory conditions
D.B. Kandel	Epidemiology and natural history of marijuana use and dependence
A.J. Budney	Marijuana as a secondary drug of abuse: clinical issues
R.S. Stephens	Treating adult marijuana dependence
C.R. Schuster	Discussant

MOTIVATIONAL ASPECTS OF DRUG ABUSE

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Over the last few years there has been increasing emphasis on the role played by motivational factors in modulating the reinforcing effects of drugs of abuse and the operational criteria for defining broad motivational concepts such as "craving". The purpose of this symposium was to provide a psychological framework for the study of motivational influences in drug abuse and to provide current examples of their application. These applications include the study of sensitization, second-order conditioning, classical conditioning of motivational stimuli and the importance of withdrawal in establishing motivation.

Schindler and Panlilio: Introduction. In recent years we have been challenged to move "beyond reinforcement" as the defining principle for behavioral studies of drug abuse. While it is clear that operant reinforcement theory cannot explain all aspects of drug-taking behavior, this approach has be successful in defining many aspects of behavior controlled by drugs of abuse. Therefore, rather than abandoning the principle of operant reinforcement, a more fruitful approach would be to expand on operant reinforcement theory to include a theory of motivation. The theory of motivation as applied to drug abuse should include the principles of motivation successfully applied to other fields of psychology. Drugs which produce withdrawal and dependence may function as internal drive stimuli, although some evidence exists that even psychomotor stimulants may have an internal drive component. Drugs which do not produce dependence may impart motivational significance through incentive stimuli. Drugs may also function as either appetitive or aversive motivators and may form either excitatory or inhibitory relationships with incentive stimuli. While incentive stimuli often appear to co-vary with discriminative stimuli, these two separate functions can be factored out with appropriate procedures. Finally, drugs may function as primary reinforcers to establish conditioned reinforcers or second-order conditioning, which can further expand their influences on behavior. The psychological area of motivation can provide a rich background for the study of drug abuse and can easily subsume processes such as craving within a well-defined scientific framework.

Schenk: Role of sensitization in the acquisition and maintenance of drug-taking behavior. Psychostimulant exposure sensitizes systems that are responsible for both the development and maintenance of cocaine self-administration. Sensitization can be demonstrated in studies where the acquisition of cocaine self-administration is measured. Latency to acquisition of self-administration is an inverse function of dose of cocaine that serves as the reinforcer. Similar to the effects of increases in dose, exposure to cocaine and other psychostimulants decreases the latency to acquisition of cocaine self-administration. These data suggest that (1) cocaine is not an inherent reinforcer for a number of subjects, but it's reinforcing effects develop as a result of repeated exposure, and (2) prior exposure to stimulants can increase the speed with which the reinforcing effects develop. A role of sensitization in the maintenance of cocaine self-administration may also be critical. During unlimited access to cocaine, the duration of cocaine self-administration is related to the number of prior cocaine self-administration sessions. Rats with a longer history of self-administration will maintain self-administration for a longer duration. Under these conditions, cocaine self-administration is at least partially maintained by the secondary reinforcing properties of cues that became associated with cocaine. Sensitization in the systems that mediate this type of sensitization may be critical for the transition to compulsive drug-taking that characterizes "abuse". It may also play a factor in relapse to drug-taking that is so prominent in cocaine abusers.

Goldberg: Second-order reinforcers as measures of the motivational properties of drugs. With human drug abusers, exteroceptive stimuli in their environment can acquire incentive-motivational significance by virtue of the association of the stimuli with drug administration. It was demonstrated many years ago that i.v. injections of various drugs of abuse can function as primary reinforcers in rats and monkeys

and that exteroceptive stimuli associated with drug injection can become established as conditioned reinforcers (or conditioned incentive-motivational stimuli). A particularly useful experimental procedure for studying this phenomenon in the laboratory is called a second-order schedule of reinforcement. Under a second-order schedule of drug self-administration, behavior (usually lever pressing) intermittently produces brief drug-associated stimuli according to one set of schedule contingencies (*e.g.,* every 30th press produces a brief light) and drug is administered in association with the stimulus according to a second set of schedule contingencies (*e.g.,* the first 30-response unit completed after 60 minutes elapses produces both the light and i.v. injection of drug). A striking feature of these schedules is that extended sequences of high rate behavior can be maintained by highly intermittent injections of various drugs, including morphine, amphetamine, nicotine, cocaine and barbiturates. However, when the brief light stimuli are omitted and presented only in association with drug injection, rates of drug-seeking behavior decrease sharply, even though the actual. frequency of. drug injection does not change. Also striking is the finding that when the brief stimuli are initially omitted during extinction (saline injections substituted for drug injections), drug-seeking behavior decreases to very low levels, but when the brief stimuli are reinstated while saline extinction continues, drug-seeking behavior immediately returns to previous high levels and remains there for several daily sessions. Using second-order schedules, the maintenance of high rates of drug-seeking behavior by drug-associated stimuli during saline extinction has been demonstrated across drug classes and in both non-human and human primates. There are clear implications of such findings for treatment of drug abuse that are now under study in many laboratories. Recently we and others have extended the use of second-order schedules of i.v. drug injection to the rat, making possible more extended neurobiological explorations of this phenomenon. Studies of second-order schedules of drug injection in subjects ranging from rats to monkeys to man will allow us to study both the control exerted over long sequences of drug-seeking behavior by conditioned reinforcing stimuli and to study the motivational consequences of the primary reinforcer, drug administration, before the drug is actually administered.

Childress: Classical conditioning as a mechanism for establishing conditioned incentives. Human drug users can experience profound arousal and drug desire when external or internal cues remind them of their preferred drug. In our view, the varied subjective and physiological responses to drug-related cues come about through a simple process of classical conditioning: cues which reliably signal drug effects can acquire the ability to trigger drug-related responses. Some of the responses to drug cues seem specific to the pharmacology of the drug class (*e.g.,* the cocaine user sensing a 'cocaine taste' in the back of the throat when seeing the street corner where cocaine is purchased); others (increased drug desire) are common to several drug classes. These responses are of clinical and research interest because they may motivate drug-seeking. We have demonstrated, under controlled laboratory conditions, that drug-related cues can trigger craving and arousal. We have used variations of this basic cue reactivity paradigm both to study and to treat cue-elicited responses. For both opiate and cocaine patients, increased "craving" is the most commonly endorsed subjective response to drug cues, and clinical interventions addressing drug craving (either through passive cue exposure or active 'anti-craving' strategies) improve drug-use outcomes in cocaine patients. These findings suggest the contributory role of drug cues in the motivation of drug-seeking and drug use. We have recently begun to use cue reactivity as a tool for examining the neurochemical and neuroanatomical correlates of cue-elicited craving states. In one approach, we assess the cue reactivity of patients receiving either placebo or cocaine "anti-craving" agents (*e.g.,* amantadine, carbamazepine, ritanserin) in the ongoing clinical trials at our Center. If a medication is identified which can block or reduce the craving/arousal to drug cues, inferences about the neurochemistry of the underlying state may be possible. Our other approach is direct: we are measuring the neuroanatomical correlates of cue-induced craving by exposing cocaine patients and controls without a cocaine history to drug cues during *in vivo* brain imaging of regional cerebral blood flow (rCBF). The salient drug-like nature of many responses to cocaine cues suggested the activated areas might be among those mediating cocaine's rewarding effects, particularly the mesolimbic brain regions. Consistent with this hypothesis, cocaine patients showed differentially increased limbic blood flow (amygdala, anterior cingulate and temporal pole) during cocaine vs. non-drug cues. Flow was not increased in several non-limbic comparison regions, and controls showed no significant differences in either subjective or rCBF response to cocaine vs. non-drug cues. These initial results suggest conditioned cue reactivity may be a useful research tool in understanding the brain substrates of drug craving and in developing interventions for compulsive drug desire.

Markou and Koob: Motivational effects of drug withdrawal. There are many sources of reinforcement in the spectrum of drug dependence that contribute to the compulsive loss of control in drug intake. However, the development of withdrawal has long been considered one of the most important and integral parts of drug dependence. More specifically, it is hypothesized that the more affective aspects of withdrawal contribute significantly more to continued drug self-administration, craving and relapse than the somatic signs of drug withdrawal. In order to investigate the neurobiology of withdrawal, several animal models of negative affective state have been developed. For example, the intracranial self-stimulation paradigm provides measures of brain reward. It has been shown that withdrawal from several drugs of abuse, such as cocaine, amphetamine, morphine and ethanol, results in significant elevations in brain reward thresholds, an effect which is opposite in direction to the acute effects of the same compounds. Furthermore, during ethanol withdrawal rats show an anxiogenic response in the plus-maze, while opiate withdrawing rats develop a conditioned place aversion to an environment paired with withdrawal. In terms of a neurobiological hypothesis of dependence, it can be conceptualized that the biological processes mediating withdrawal have developed as counter-adaptations to the acute effects of drug. These counter-adaptations could be either within-system adaptations or between-systems adaptations. For example, decreases in extracellular levels of dopamine and serotonin in the nucleus accumbens of rats during cocaine withdrawal are considered within-system adaptations, while elevations in extracellular levels of CRF in the amygdala of cocaine or ethanol withdrawing rats can be considered between-systems adaptations. The extended amygdala is a neural system that may mediate both the acute reinforcing effects of drugs and drug withdrawal (*i.e.,* negative reinforcing properties) through both within- and between-system adaptations. Such neuroadaptations could constitute the neurobiological substrate of phenomena associated with drug dependence, such as loss of control over drug use, drug withdrawal, craving and relapse.

Stolerman: Discussion. In the simplest case, the motivation to take drugs may be the result of previous exposure to drugs that served as positive reinforcers. There is no clear limit to the power of this reinforcing event but in addition, the discriminative and aversive stimulus effects of drugs must be built into an integrated concept that recognizes the malleability of drug action as a function of environmental and genetic factors. Craving may be the subjective expression of the combined impact of the psychopharmacological processes in the concept; it is only one of several potentially important cognitive events and its influence on drug-taking is for research to demonstrate. Thus, craving is the result of multiple environmental and genetic effects associated with the complex phenotype that we call drug dependence; craving is not a monolithic entity that offers a single molecular target for pharmacotherapy. A strong feature of the studies presented on sensitization was that they attempted to examine self-administration rather than some other arbitrary response to the drug. An important question is the role of tolerance to the aversive effects of a drug in producing the apparent sensitization to reinforcing effects. Broader questions remaining on sensitization include the need for an agreed definition; it may result from either a left-ward or an upward shift in the dose-response curve, which carry very different implications for drug-taking. Similarly, the study of classical conditioning in drug-taking must take into account the role of operant conditioning; drug-taking is an operant and the way classical conditioning interacts with that operant has to be defined. For example, a conditioned stimulus may also serve a discriminative function in setting the occasion for drug-seeking. Attention was drawn to a way in which compounding of conditioned stimuli increased the strength of drug-taking. Withdrawal phenomena appear to provide motivation through unique aversive processes. Aversive stimuli are thought to have three functions; they can serve as negative reinforcers and as punishing stimuli, and they can support place and taste aversions that give an indirect indication of aversive events. While withdrawal from morphine-like opioids meets all of these criteria, there is a need for more evidence on whether withdrawal from many non-opioid drugs does so. In summary, the development of more sophisticated psychopharmacological models of drug-taking was an important trend, and the need to integrate diverse strands of existing knowledge was emphasized. Care must be taken to avoid rediscovering old knowledge and renaming old, discarded concepts with new terminology; specific, unique and testable predictions are required to advance the field.

EXCITATORY AMINO ACIDS IN STIMULANT ABUSE AND AIDS DEMENTIA

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This symposium included four presentations covering the role of excitatory amino acids in the neurotoxicity associated with AIDS and with stimulant abuse. The first presentation by S. Lipton reviewed the role of the NMDA receptor in neuronal injury in AIDS. As many as 70% of AIDS patients develop neurological complications, but neurons themselves are not infected by HIV. It appears that HIV- or immune-related toxins may directly or indirectly lead to neuronal injury via an interaction of macrophages (microglia) and astrocytes with neurons. The final common pathway involves voltage dependent calcium channels and NMDA receptor operated channels. These calcium channels are opened by excitatory amino acids such as glutamate and possibly by direct stimulation of the HIV coat protein (GP120). When opened, calcium flows into neurons via these channels, and this intraneuronal calcium load can be toxic leading to apoptosis. lnfected macrophages or microglia may release an NMDA-like neurotoxin that either binds directly to the neuronal NMDA receptor or to astrocyte receptors. These astrocytes can produce quinolinic acid, another excitatory amino acid. Treatments based on this model of neurotoxicity include antagonists of the L-type voltage dependent calcium channels such as nimodipine and of the NMDA receptor such as MK801. Activation of both types of channels appears necessary for AIDS neurotoxicity and both are activated by glutamate-like agonists. In general, the sensitivity to glutamate may be enhanced by GP120, possibly because infected macrophages secrete quinolinic acid. Other therapeutic approaches are to block the CD4 receptor which may bind not only the GP120, but also vasoactive intestinal peptide (VIP). A VIP analog, peptide T has been developed to block this binding, and it has shown efficacy in preliminary human studies. Thus, three pharmacological interventions are suggested to protect neurons from HIV related injury: calcium channel or NMDA antagonists and VIP congeners.

The second presentation reviewed the work of M. Heyes on quinolinic acid levels in the cerebrospinal fluid (CSF) of AIDS patients. The CSF levels are substantially elevated in AIDS patients to as much as 20 fold among those with AIDS dementia compared to normal controls. The CSF elevations are also substantially greater than the relative elevations in blood levels of quinolinic acid. Normally, CSF levels are less than 10% of blood levels, but in AIDS dementia, CSF levels are even higher than blood levels. This reflects a substantial increase in brain production of quinolinic acid by glial cells as a product of brain serotonin metabolism. Quinolinic acid is released from these microglia as well as from neurons and it then diffuses into the CSF. The duration of quinolinic acid exposure may determine neurotoxicity, with corticostriatal neurons in rats degenerating after about 50 days of quinolinic acid exposure. Basal ganglia neurons seem particularly sensitive to this toxicity, and there is prominent invasion of macrophages and extensive microglia activity in the basal ganglia of AIDS dementia patients reflecting the production of quinolinic acid. The severity of AIDS dementia is correlated with these CSF levels of quinolinic acid ($r=0.43$, $P<0.0001$) and the highest correlations were with learning and immediate recall tasks. The quinolinic acid levels in CSF can be reduced substantially by AZT treatment (11 fold reduction), which can also improve neuropsychological functioning. Thus, improvements in neurological impairment as well as prevention of subsequent neuronal damage are correlated with reductions in CSF quinolinic acid levels consistent with its neurotoxicity.

L. Gold presented on transgemic mice that express either the GP120 protein or interleukin 6 (IL6) in brain astrocytes. This IL6 peptide is secreted by HIV infected microglia and astrocytes and may contribute to AIDS neurotoxicity. These mice have many characteristics of AIDS dementia in humans, particularly those mice expressing IL6. In addition, these IL6 mice have abnormal NMDA receptor function suggesting increased calcium permeability as a mechanism for neurotoxicity. Ongoing work also suggests enhanced drug self-administration in these IL6 mice.

The presentation by P. Sonsalla focused on the role of NMDA receptors and excitatory amino acids in the dopaminergic (DA) neurotoxicity produced by stimulants particularly amphetamine. The mechanism inducing dopamine neuron damage may involve an increase in free radical production from dopamine oxidation (*e.g.* 6-hydroxydopamine). Various NMDA antagonists can prevent amphetamine neurotoxicity. The protective effects of NMDA antagonists may be due to an attenuation of DA release as well as direct activation of NMDA receptors located on the DA nerve terminal. However, nerve terminals, not cell bodies are damaged by amphetamine, and NMDA toxicity affects cell bodies, while sparing nerve terminals. Thus, glutamate and NMDA receptors may be critically involved in this stimulant neurotoxicity, perhaps through the hyperthermia produced by all stimulants (*e.g.* amphetamines and cocaine) in humans leading to metabolic stress and toxic oxidation by products.

The final presentation by T. Kosten reviewed human studies from substance abusers with HIV infection and built on the previous presentations that excitatory amino acid induced damage to neurons may underlie the cognitive impairments found in patients with AIDS or with stimulant abuse. The reasons for activation of the excitatory amino acid system and its neurotoxicity differs somewhat between AIDS and stimulant abuse. In AIDS, the HIV virus may induce release of various cytokines through the GP120 coat protein leading to stimulation of excitatory amino acid release. In stimulant dependence, excitatory amino acid release may be related to dopaminergic neuronal interactions with neurons that release excitatory amino acids as well as to indirect effects of brain ischemia from stimulant induced vaso-constriction and platelet aggregation. Stimulant induced brain ischemia can be shown by blood flow neuroimaging studies.

The assessment of cerebral blood flow using SPECT or PET has demonstrated patchy perfusion defects in the brains of both AIDS patients and in cocaine abusers. The cortical perfusion defects produced by these two disorders are indistinguishable in appearance, but a distinguishing feature between early AIDS infection and cocaine induced neuronal toxicity occurs in the basal ganglia. Cocaine abusers also have patchy perfusion defects in the basal ganglia, but early AIDS patients more commonly have hyperperfusion of the basal ganglia. We have found that these basal ganglia perfusion abnormalities are correlated with neuropsychological impairment. In substance abusers with AIDS, increased levels of perfusion in the basal ganglia are correlated with increased neuropsychological impairment. Conversely, in cocaine abusers who are not HIV infected, decreased levels of basal ganglia perfusion are correlated with increased neuropsychological impairment. Thus, in severe cases of neuropsychological impairment, cocaine abusers tend to have decreases in basal ganglia perfusion whereas substance abusers with AIDS tend to have increased levels of basal ganglia perfusion.

As AIDS dementia progresses, brain perfusion including perfusion of the basal ganglia is globally reduced. Autopsy studies of AIDS patients frequently show substantial destruction of the basal ganglia and its dopaminergic projections from both the ventral tegmental area and substantia nigra. Damage to these same systems has been suggested by recent studies of cocaine abusers who have demonstrated Parkinsonian symptoms during cocaine absence. Thus, stimulant abusing AIDS patients may be particularly vulnerable to neurotoxicity in these dopaminergic systems leading to cognitive impairment.

Treatment of the HIV infected cocaine abuser with antivirals such as AZT for their AIDS induced perfusion defects and with anti-platelet agents such as aspirin for their cocaine induced perfusion defects are two approaches to improving their cognitive functioning and possibly their response to cocaine psychotherapies. However, an alternative approach to treating both disorders in these patients might use excitatory amino acid antagonists such as mementine or lamotrogine. While mementine is not currently available in the United States, studies have been done with a related compound amantadine. Studies with amantadine in cocaine abusers have had mixed results, although some show promise in reducing cocaine abuse. More recently, studies have begun with lamotrogine in methadone-maintained HIV infected cocaine abusers. Lamotrogine has demonstrated good patient acceptability and compliance with once daily dosing as well as excellent safety in human laboratory studies with cocaine administration. In an initial clinical trial, lamotrogine reduced cocaine use. In addition, these HIV positive cocaine abusers who become abstinent showed significant improvement in neurocognitive functioning.

In summary, both AIDS and stimulant abuse appear to induce neuronal toxicity through a final common pathway involving excitatory amino acids. This neuronal damage can be carefully monitored using SPECT blood flow neuroimaging, which can demonstrate not only patchy perfusion defects at baseline, but also good responses to specific treatment interventions such as AZT and aspirin. A new treatment approach that addresses both disorders is the use of excitatory amino antagonists such as lamotrogine.

The discussant, P. Bridge, reviewed the medication development implications of this work for both cocaine abuse and AIDS cognitive impairment.

AGONIST EFFICACY, DRUG DEPENDENCE, AND MEDICATIONS DEVELOPMENT

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INTRODUCTION

Many drugs of abuse produce behavioral effects, directly or indirectly, by actions at membrane-bound receptors. Current concepts of agonist efficacy in receptor theory may be useful for evaluating these receptor-mediated effects and for developing medications to treat drug abuse. Concepts of efficacy have evolved steadily throughout the development of receptor theory. At least as early as the 1870s, Langley suggested that the actions of chemicals on biologic tissues were governed by the law of mass action. Others subsequently showed orderly relationships between the effects of agonists and their antagonism by receptor blockers, providing support for the notion that drugs produced effects by acting at specific receptors. In the 1920s Clark offered his classic theory of drug action, based on the fundamental premise that the magnitude of response was proportional to the fraction of receptors that was occupied. It became evident, however, that some drugs produced maximal effects at concentrations that did not occupy all of the receptors and that other drugs produced less-than-maximal effects even when occupying all receptors. In the 1950s, Ariens introduced the term *intrinsic activity,* defined as the property of an agonist that produced an effect per drug-receptor interaction. The postulation of intrinsic activity provided a parsimonious explanation for variations in responses obtained with drugs that had similar affinities. Yet, it did not account for the empirical observation that some drugs were full agonists under some conditions and partial agonists, or perhaps even antagonists, under other conditions. Presumably, intrinsic activity (as postulated by Ariens) was an inherent property of the chemical structure of the drug and the receptor and should not vary among tissues. Stephenson and, later, Furchgott were among those to address this issue of different tissue-dependent responses to the same drug. In particular, Furchgott introduced the term *intrinsic efficacy,* proposing that efficacy was a product of the intrinsic efficacy of the drug and the population of active receptors. This proposition continues to be advocated in contemporary pharmacology. A noteworthy corollary to this proposition is the idea of spare receptors for a given response. Thus, a drug might be a full or partial agonist under selected conditions, depending on whether there are a sufficient or insufficient number of receptors to mediate a full response. Strong empirical support for this view of drug efficacy has come from studies with irreversibly-acting antagonists (see below) and has strengthened the corollary of spare receptors.

OPIOIDS AND EFFICACY

Comparisons of the efficacy of agonists across procedures that may predict therapeutic and, separately, adverse effects of a drug can be a useful strategy in medications development. For example, the effects of morphine-like opioids have been compared in thermal antinociception studies to predict analgesic effects and in drug discrimination experiments to predict abuse potential. In both procedures, increases in stimulus intensity are thought to increase the efficacy requirement, *i.e.,* the number of receptors that need to be activated for an agonist effect. When the temperature of the thermal stimulus in the antinociception assay was increased, morphine and other opioids with moderate or high efficacy at the *mu*-opioid receptor continued to exert a maximum effect whereas lower efficacy drugs, such as pentazocine and nalbuphine, became inactive. Similarly, pentazocine and nalbuphine substituted fully for a low training dose of morphine and only partially for a 10-fold higher training dose in drug discrimination procedures, indicative of low agonist efficacy. Another approach to the assessment of relative efficacy has been to down-regulate the *mu*-opioid receptor population either functionally, by inducing tolerance and cross-tolerance, or physically, by administering a ligand that binds to the receptor irreversibly (*e.g.,* the opioid antagonist -funaltrexamine). In both types of experiments, the apparent efficacy of opioid drugs was lower in producing antinociceptive effects than

morphine-like discriminative stimuli. Evidence such as this suggests that morphine-like opioids have higher apparent efficacy in animal models predictive of abuse potential than therapeutic (analgesic) effect, If this same efficacy relationship applies in humans, it may be difficult to develop new *mu*-opioid analgesic agents that lack abuse potential. Moreover, abuse-related effects of *mu*-opioid agonists are likely to persist under conditions that diminish therapeutic activity, such as drug tolerance.

PSYCHOMOTOR STIMULANTS AND EFFICACY

Cocaine and related stimulant drugs act as indirect dopamine agonists by increasing levels of synaptic dopamine, and the development of therapeutics has been aimed at the receptor-mediated effects of dopamine as well as the indirect actions of stimulants. One benefit of the first approach is the possibility that, as in the treatment of addiction to opioid drugs, differences in agonist efficacy can be exploited to develop different types of medications. Recent evidence, primarily from observational studies and from studies of the rate-altering, discriminative-stimulus, and reinforcing effects of drugs in monkeys, confirms this possibility. Thus, D1 agonists with high efficacy (*e.g.,* dihydrexidine or SKF 81297) appear to have behavioral effects that overlap, but do not completely reproduce, those of cocaine or methamphetamine. Like psychomotor stimulants, these drugs produce dose-related increases in visual checking in observational studies and may substitute at least partially for cocaine or methamphetamine in drug discrimination experiments. Unlike cocaine and other psychomotor stimulants, however, D1 agonists do not increase lever pressing under fixed-interval schedules and may maintain i.v. self-administration behavior under relatively restricted conditions. The incomp1et.e overlap in behavioral effects of D1 agonists with high efficacy and stimulant drugs may be a favorable profile of action in treatment programs employing substitution strategies to treat cocaine or other stimulant abuse.

D1 agonists with low efficacy appear to have behavioral effects that differ qualitatively from those of D1 high-efficacy agonists and are comparable to those of dopamine D1 receptor blockers. Both D1 receptor blockers and low-efficacy agonists decrease activity and, at doses that markedly disrupt normative behavior, can surmountably antagonize the behavioral effects of psychomotor stimulants such as cocaine or methamphetamine. However, ongoing studies are indicating that D1 agonists with presumably intermediate agonist efficacy may surmountably antagonize behavioral effects of stimulants at doses smaller than those that markedly disturb behavior. These are exciting findings that suggest it may be possible to develop D1 partial agonists with a pragmatically desirable separation between therapeutic actions and compliance-limiting (*e.g.,* adverse) effects.

On a different tack, differences in apparent efficacy of indirect dopamine agonists at the dopamine transporter have been proposed to account for differences in the degree to which various dopamine uptake inhibitors produce effects like those of cocaine. It has been suggested that indirect agonists with limited efficacy at the dopamine transporter may function like partial agonists and prevent the full effects of cocaine, while acting as weak stimulants. Though a second messenger system has not been identified for the inhibition of dopamine uptake, the manner in which compounds inhibit dopamine uptake could vary, resulting in differences in their effectiveness. As one example, binding of an uptake inhibitor with the transporter could alter the cycle time of the transporter with different cycle times producing effects of varying magnitude. Despite its attractiveness, the postulation of partial agonists at the transporter is not well supported by experimental evidence. *In vitro,* virtually all uptake inhibitors completely inhibit uptake at the highest concentrations, and none exhibit a plateau at less than 100% inhibition. Some investigators have analyzed the ratio of K_i values for binding to the dopamine transporter and IC_{50} values for dopamine uptake inhibition, reasoning that a compound with a relatively high IC_{50} value might function as an antagonist at the dopamine transporter (the so-called “dopamine-sparing cocaine antagonist”). Unfortunately, ratio values are typically provided without statistical indications of significance, making them especially difficult to compare and interpret. Because compound potencies (and, therefore, ratio values) can vary among assay conditions, and because binding studies are conducted at equilibrium and uptake studies are not, these types of comparisons are tenuous, at best. To date, compounds with high ratio values have not been unambiguously distinguished from those with low ratio values with regard to their pharmacology.

In contrast to *in vitro* approaches, studies employing *in vivo* procedures have provided results more consistent with the notion of differences in intrinsic efficacy among dopamine uptake inhibitors. For example, studies on extracellular dopamine levels in brain have suggested that the selective dopamine uptake inhibitor GBR12909 may be a partial agonist and, thereby, a functional cocaine antagonist. In behavioral studies, a variety of compounds have been assessed for their effects on dopamine uptake, using doses that produced equivalent *in vivo* dopamine transporter occupancy. The degree of locomotor stimulation showed an appreciable variability across drugs. Conversely, others have reported that doses of several uptake inhibitors produced comparable stimulant effects at different levels of transporter occupancy. Because of the different relations between dopamine transporter occupancy and effects for various uptake inhibitors, these results suggest that there are differences in efficacy among the dopamine uptake inhibitors.

Interpreting these *in vivo* results, however, must be done cautiously. The dose-effect curve for stimulation of locomotor activity is bitonic with maximal effects generally occurring at intermediate doses. The inflection of the curve is often attributed to the emergence of high-dose effects that interfere with the expression of locomotor activity and that may be mediated by different mechanisms. In this case, different relative potencies for stimulant and interfering effects among the particular compounds may result in apparent differences in their effectiveness as stimulants. A lesser maximal effect may simply represent greater relative potency for producing interfering effects rather than differences in efficacy. This type of apparent difference in efficacy may occur with any complex behavior, including drug discrimination and self administration. Therefore, conclusions regarding differences in intrinsic efficacy must be made cautiously. In all cases, the specific criteria of partial agonism (see below) should be satisfied before considering alternate interpretations such as indirect dopamine agonism or partial agonism.

BENZODIAZEPINES AND EFFICACY

Clinically-used benzodiazepines, which may induce dependence even at therapeutic doses, act as full efficacy (full agonist) positive allosteric modulators of the actions of GABA at several GABA, receptor subtypes. More recently-developed compounds bind to the same sites, but may act selectively or with partial agonist properties. For example; the mixed (full/partial) agonist abecamil, like benzodiazepines, has anxiolytic and anticonvulsant effects; unlike benzodiazepines, it is without muscle relaxant effects and produces little sedation. One explanation for such a profile of action is that abecamil acts as a partial agonist at some benzodiazepine receptor subtypes and as a full agonist at other subtypes. Whether a benzodiazepine receptor ligand acts at a particular GABA receptor subtype is partly dependent on the isoform making up the receptor. Classical benzodiazepines such as diazepam bind with similar affinity to receptor subtypes containing 1, 2, 3, and 5 isoforms and with low affinity at 4- and 6-containing subtypes. Abecamil shows higher affinities for l-containing receptors than for the other subtypes; equally importantly, abecamil may additionally act as a full agonist at certain receptors but a partial agonist at others. Consistent with this view, studies of the ability to potentiate GABA-induced chloride currents in frog oocytes expressing 1 1 2, or 5 1 2 subunit combinations reveal an efficacy of abecarnil similar to diazepam in the former, but less than diazepam in the latter. Both abecarnil and non-selective agonists like bretazenil have shown reduced dependence liability in animals studies. In one study, mice were treated for 12 days with 6 mg/kg/12 hr of the benzodiazepine alprazolam and subsequently for 7 additional days with either vehicle, abecarnil (6 mg/kg/day) or the same dose of alprazolam. When treatments were terminated mice that had received alprazolam for 12 or 19 days showed seizures, increased muscle tone and anxiety. Abecarnil prevented withdrawal signs in mice that had received chronic alprazolam and no withdrawal signs were observed when daily administration of abecarnil was terminated. These experiments indicate that a compound which acts as a mixed full/partial agonist at a subpopulation of benzodiazepine receptors may give rise to a profile of cross tolerance different from that of a nonselective benzodiazepine, and may prevent the occurrence of withdrawal following chronic treatment with a benzodiazepine. Nevertheless, clinical experience with the partial and/or selective agonists in terms of their ability to produce withdrawal effects or to treat benzodiazepine withdrawal has been mixed. Alpidem given together with a reduced dose of benzodiazepine during withdrawal exacerbated symptoms, though this may reflect methodological rather than conceptual problems. Using a different design, parallel to that used in animal experiments, abecarnil was found to be useful in weaning mildly dependent patients off benzodiazepines.

PARTIAL EFFECTS IN DRUG DISCRIMINATION AND EFFICACY

Because of its pharmacological specificity and sensitivity, drug discrimination constitutes a powerful tool to characterize *in vivo* agonist and antagonist properties of compounds. Some compounds, however, neither fully substitute for nor completely antagonize the training drug, but produce intermediate responding. It is helpful to assume initially that such an outcome results from low efficacy actions at the receptors that mediate the discriminative stimulus effects of the training drug. This hypothesis can be examined further in several ways. One approach is to examine whether a compound that produces intermediate responding when given alone, partially antagonizes the training drug. Another is to vary the apparent sensitivity of the discrimination by, for example, varying the training dose, training to discriminate the training dose from a lower dose of the training drug, noncontingent administration of doses higher than the training dose, noncontingent administration of an antagonist of the training drug, or by using different reinforcement contingencies during drug and saline training sessions.

In experiments in animals trained to discriminate opioids from saline, some of these approaches were used to compare the intermediate responding produced by partial opioid agonists, such as cyclazocine, with that produced by phencyclidine (PCP)-like N-methyl-D-aspartate antagonists, such as dizocilpine. Unlike cyclazocine, the effects of dizocilpine were not consistent with characterization as a low efficacy agonist at opioid receptors. Further, dizocilpine produced intermediate responding not only in opioid-trained animals, but also in a variety of pharmacologically unrelated drug discriminations. This intermediate responding was frequently associated with a particular pattern of other behavioral effects (*i.e.,* a high percentage of responses on the non-selected lever, both before and after lever selection occurred, and a long selection latency) that differed from patterns observed with drugs that likely produce intermediate responding by partial agonist actions. Thus, the intermediate responding produced by PCP-type drugs often appears to involve pharmacological effects that differ from those of the training drug, and behavioral mechanisms unrelated to stimulus generalization. Although efficacy at the receptors that mediate the discriminative stimulus effects of the training drug has been shown to explain many of the instances of intermediate responding in drug discrimination, certain outcomes, exemplified by those obtained with PCP-type drugs, are less readily accommodated. Such outcomes do not appear to offer valid measures of efficacy at the receptors mediating the discriminative stimulus effects of the training drug, and require behavioral analyses that are more detailed than those that are commonly used.

SUMMARY AND CONCLUSIONS

The term EFFICACY may be used in various ways to describe sometimes unrelated phenomena. For example, clinical efficacy refers to the therapeutic potential of drugs, irrespective of mechanism. Agonist efficacy, as discussed here, refers to the ability of a drug to initiate a response after binding to a receptor; agonist efficacy and clinical efficacy can be, though arc not necessarily, related. On a cellular level, it is now clear that, in some systems, receptors exist in at least two different states. Different states can influence the coupling of drugs and receptors; moreover, receptors can change from one state to another, thereby altering the likelihood that particular drugs will bind to them. The relative affinity of a drug for different conformations of the same receptor type in a given system may partly determine apparent efficacy, i.e., whether a drug acts as agonist, antagonist or, perhaps, partial agonist. The basic notion that the actions of agonists can vary in a predictable manner across conditions, though exceedingly complicated when evaluated *in vivo,* has been instructive for understanding the relative importance of agonist efficacy in pharmacologic effects of a variety of drugs, including drugs of abuse. The central issue is what can the notion of efficacy tell us about drug dependence and how can it facilitate the development of medications for treatment of drug dependence. An underlying premise of this paper has been that rational, empirically-guided development of new medications for the treatment of drug abuse necessitates that the mechanism of action of the abused substance be well characterized.

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DRUGS OF ABUSE AND GENDER DIFFERENCES

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The importance of gender differences has been highlighted by the recent focus on women and health and the NIH initiative to include women in research. We have become increasingly aware that we can no longer study a population of solely men 2nd generalize the findings to women. This symposium clearly demonstrated that the women may respond differently to drugs of abuse. Gender differences occur in responsivity to drugs on a cellular level, on subjective and behavioral levels, and in response to pharmacological treatments. This symposium explored the up-to-date scientific findings on gender differences in response to nicotine, cocaine and sedatives. It also examined the role of gender in co-morbid disorders among substance abusers.

Dr. Kenneth Perkins presented a review of results from nicotine replacement trials that indicates that nicotine gum or patch appears to be less effective in. women than men (Perkins 1996). One possible explanation is that nicotine intake may be less reinforcing in women vs. men, while non-nicotine aspects of smoking may be more reinforcing. Recent research suggests that nicotine self-administration is less robust in women, nicotine pre-loading has less effect in attenuating smoking in women, and women may be less sensitive to the discriminative stimulus effects of nicotine. In contrast, women may be more responsive to other stimuli accompanying smoking (taste, smell, etc.). These findings are consistent with research from the field of psychophysiology reliably showing that women are less accurate than men in detecting physiological changes (*i.e.* interoceptive stimuli). If additional research confirms this sex difference, nicotine replacement may be less warranted in the treatment of women, while interventions to counter other reinforcing aspects of smoking may deserve greater attention.

Cocaine research on gender-related differences has also found reduced response to cocaine in females compared with males. Previous results have shown that cocaine is more toxic to male rats and in ovariectomized female rats (Selye 1971; Morishima *et al.* 1993), and estradiol administration protects male rats from toxicity (Selye 1971) and reduces cocaine toxicity in female rats (Rapp *et al.* 1979). Other evidence showing reduced effects of cocaine in females include cocaine self-administration paradigms in which female rats reach higher breakpoints than male rats, particularly during estrus (Roberts *et al.* 1989). These findings may be due to lower plasma cocaine levels observed in females compared to male rats (Rapp *et al.* 1979). Dr. Scott Lukas conducted a study to determine if there are sex-related differences in humans as well. The sample was comprised of seven healthy male and seven healthy female volunteers, each who used cocaine on the average of six times per year. Male subjects attended two visits during which time they received placebo cocaine and 0.9 mg/kg of intranasal cocaine. Females were given the same doses but during the follicular and luteal phases of their menstrual cycle, resulting in four visits. The results from this study showed that the male subjects achieved a higher plasma cocaine level than females and experienced more intense behavioral effects than females. However, the females experienced similar cardiovascular effects as the males. Possible mechanisms for these sex differences include a reduced absorption of cocaine due to increased nasal mucosa thickness/viscosity in females, particularly when estrogen levels are high (Taylor 1961) or higher levels of cholinesterase activity in females (Sidell and Kaminskis 1975). Both of these mechanisms would result in reduced levels of cocaine in women compared to men. Because the women achieved similar increases in heart rate, but at much lower plasma cocaine levels, they may be more sensitive to the cardiovascular effects of cocaine.

Few epidemiological studies of abuse or therapeutic use of benzodiazepines attempt to address questions about sex differences. It is not known whether acute responses to benzodiazepines are different between men and women. Recent basic science research demonstrates that ovarian hormone metabolites and benzodiazepines may

share receptor sites in the CNS (Majewska 1986) and therefore fluctuations in ovarian hormones might influence the pharmacodynamic response to benzodiazepines in women. Moreover, hormones might influence the pharmacokinetics of benzodiazepines. For example, it has been found that clearance of some benzodiazepines is slower in women compared to men (Greenblatt *et al.* 1980, Divoll *et al.* 1981). Ovarian hormones have been implicated in this sex difference: low dose oral contraceptives delay elimination of several benzodiazepines (Abemethy *et al.* 1982, Stoehr *et al.* 1984) and women who use oral contraceptives are more sensitive to the psychomotor-impairing effects of benzodiazepines (Kroboth *et al.* 1985). Few studies have investigated whether the hormonal changes across the menstrual cycle influence responses to benzodiazepines or other drugs. Drs. Margaret Rukstalis and Harriet de Wit examined pharmacokinetic and pharmacodynamic responses to a short acting benzodiazepine, triazolam, at three hormonally distinct phases of the menstrual cycle: follicular (6-8 days after menstruation); ovulatory (within 48 hours of the onset of LH surge); and luteal (6-8 days after the onset of LH surge). They examined subjects' responses in relation to their levels of estradiol, progesterone and a metabolite of progesterone, allopregnanolone. Triazolam (0.25 mg po) or placebo was administered in double-blind fashion to twenty non-smoking healthy normally-cycling female volunteers aged 18-35. Dependent measures included a check list of subjective state, psychomotor tests, a visual analog liking questionnaire, and plasma levels of drug collected over 12 hours. Triazolam increased subjective reports of "feel drug" and impaired psychomotor performance but these effects did not vary across phases of the menstrual cycle. Pharmacokinetic parameters of triazolam did not vary across the menstrual cycle. Therefore, the physiologic concentrations of circulating ovarian hormones across the menstrual cycle did not significantly influence the pharmacokinetic, subjective or behavioral responses to a low dose of the benzodiazepine triazolam. The failure to find menstrual cycle differences may be due to the dose of triazolam that was used in the study. Further research is needed to compare responses to psychoactive drugs in men and women to determine whether clinically significant differences exist, including sex !differences in tolerance or dependence/withdrawal.

Another area of importance with regard to gender difference in substance use disorders is that of psychiatric comorbidity. A number of studies have commented on socioeconomic and psychological differences between men and women in substance abuse treatment. There arc also clearly gender-specific differences in the societal response to substance abuse in women which may be a contributing factor to any increased risk for psychopathology. Studies have consistently reported more Axis I psychopathology in women substance users as compared to men. In the current presentation by Dr. Kathleen Brady, gender comparisons in data collected from 100 treatment-seeking substance users (50 men/50 women) were discussed. Women were more likely to have another Axis I disorder ($p<0.05$), in particular anxiety disorders ($p<0.05$), but these differences were not substantially different from gender differences in the general population for psychiatric disorder.

A number of studies, including this one, have found, however, that gender differences in psychopathology are more pronounced in alcohol-dependent individuals than in cocaine or opiate dependent individuals (Rounsaville *et al.* 1991; Rounsaville *et al.* 1982). For example, alcoholic women in the current study were two times more likely to have depression when compared to alcoholic men, while the rates of depression in cocaine dependent men and women were approximately equal. It is difficult to say at this point whether these differences reflect the differential pharmacologic activity of these drugs of abuse. Clearly this is an area ripe for further investigation.

Another important area in the exploration of gender differences in the cormorbidity of substance use and psychiatric disorder is in gender differences in order of onset of psychiatric disorder and substance *use* disorder between men and women. Several studies (Dunne *et al.* 1993) including this one, demonstrate that in women the psychiatric disorder is more likely to precede the substance use disorder than in men.

This suggests a possible gender-specific etiologic relationship between substance use disorders and psychiatric disorder which could have important treatment implications. Further exploration of this important area is also indicated.

Dr. Cora Lee Wetherington, Women's Health Coordinator at the National Institute on Drug Abuse, presented drug use prevalence data from national surveys (National Household Survey on Drug Abuse and Monitoring the Future) indicating that for some drugs the gender gap in drug use is quite large, for others the gap is quite narrow, and for still others, there is no gender gap. She also presented survey data showing gender differences in the consequences of drug abuse such as data from the DAWN survey showing discrepancies in the male/female ratio of emergency room episodes and deaths, relative to the prevalence of male/female drug use. The survey statistics raise questions about why any gender gaps occur at all. Dr. Wetherington cited laboratory, field and clinical research that is beginning to suggest gender differences in the biological factors in drug abuse, in the initiation and progression to drug use and abuse, the antecedents and consequences of drug use and abuse, and prevention and treatment efforts. The existing research base on gender differences in drug use is unfortunately quite small. It serves nevertheless to highlight the pervasive need for gender-based research in all areas of drug abuse in order to ensure that research produces findings that are applicable to both males and females.

REFERENCES

Abernethy, D.R.; Greenblatt, D.J.; Divoll, M.; Arendt, R.; Ochs, H.R.; and Shader, R.I. Impairment of diazepam metabolism by low-dose estrogen oral-contraceptive steroids. NEJM 1982;306:791-792

Divoll, M.; Greenblatt, D.J.; Harmatz, J.S.; and Shader, R.I. Effects of age and gender on disposition of temazepam. J Pharm Sci 1981;70:1104-1107

Dunne, F.J.; Galatopoulos, C.; and Schipperheijn, J.M. Gender differences in psychiatric morbidity among alcohol misusers. Comprehensive Psychiatry 1993;34:95-101

Greenblatt, D.J; Divoll, M.; Harmatz, J.S.; and Shader, R.I. Oxazepam kinetics: effects of age and sex. J Pharmacol Exp Ther 1980;215:86-91

Kroboth, P.D.; Smith, R.B.; Stoehr, G.P.; and Juhl, R.P. Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. Clin Pharmacol Ther 1985;38:525-532

Majewska, M.D.; Harrison, N.L.; Schwartz, R.D.; Barker, J.L.; and Paul, S.M. Steroid hormone metabolites are barbiturate-like modulators of the GABAA receptors. Science 1986;232:1004-1007

Morishima, H.O.; Abe, Y.; Matsuo, M.; Akiba, K.; Masaoka, T.; and Cooper, T.B. Gender-related differences in cocaine toxicity in the rat. J Lab Clin Med 1993;122:157-163

Perkins, K.A. Sex differences in nicotine versus nonnicotine reinforcement as determinants of tobacco smoking. Exp Clin Psychopharmacol 1996;4:166-177

Rapp, U.; Kourounakis, P.; and Selye, H. Effects of steroids and diethylstilbestrol on cocaine toxicity, plasma concentrations and urinary excretion. Arzneim.-Forsch./Drug Res. 1979;29:48-50

Roberts, D.C.S.; Bennett, S.A.L.; and Vickers, G.H. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Neuropsychopharmacologv 1989;98:408-411

Rounsaville, B.J.; Anton, S.F.; Carrel, K.; Budde, D.; Prusoff, B.A.; and Gawin, F. Psychiatric diagnosis of treatment-seeking cocaine abusers. Arch Gen Psychiatry 1991;48:43-51

Rounsaville, B.J.; Weissman, M.M.; Kleber, H.; and Wilber, C. Heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch Gen Psychiatry 1982;39: 161-166

Selye, H. Protection by estradiol against cocaine, coniine, ethylmorphine, LSD, and strychnine. Horm Behav 1971;2:337-341

Sidell, F.R. and Kaminskis, A. Influence of age, sex, and oral contraceptives on human blood cholinesterase activity. Clin Chem 1975;21:1393-1395

Stoehr, G.P.; Kroboth, P.D.; Juhl, R.P.; Wender, D.B.; Phillips, J.P.; and Smith, R.B. Effect of oral contraceptive on triazolam, temazepam, alprazolam and lorazepam kinetics. Clin Pharmacol Ther 1984;36:683-690

Taylor, M. An experimental study of the influence of the endocrine system on nasal respiratory mucosa. J Laryngol Otol 1961;75:972-977.

PRESYNAPTIC AND POSTSYNAPTIC NEUROCHEMICAL ALTERATIONS IN HUMAN PSYCHOSTIMULANT ABUSERS

J.K. Staley and Y.L. Hurd.

Understanding the neurochemical basis and sequelae of psychostimulant abuse is fundamental for the development of effective pharmacotherapies for the treatment of addiction. The classical psychostimulants amphetamine and cocaine, both indirect-acting dopamincrgic agonists, elevate dopamine (DA) through distinct interactions with the plasma membrane DA transporter. The resulting transient elevation of DA activates feedback pathways and initiates a sequence of neuroadaptive alterations of pre- and postsynaptic neuronal systems that mediates the psychotropic and reinforcing actions of psychostimulants. These compensatory neurochemical alterations vary throughout the development of the drug addiction disorder and thus contribute to the vast complexity of addiction. Considerable progress is currently being made in delineating the neurochemical alterations that occur with chronic psychostimulant abuse through direct *in vivo* and postmortem neurochemical studies of human psychostimulant abusers. This symposium highlights the adaptations of four neurochemical systems in human cocaine abusers- DA, opioid peptides, gamma-amino-butyric acid and serotonin.

Robert T. Malison - SPECT Imaging of Pre- and Postsynaptic Dopamine Function in Human Cocaine Abusers. Postmortem studies of cocaine overdose victims have suggested elevations in striatal dopamine transporters (DAT) relative to healthy controls. Single photon emission computed tomographic (SPECT) neuroreceptor imaging methods were used to examine whether striatal DAT are increased in acutely abstinent (96 hr) cocaine addicts as compared to age-, gender- and ethnically-matched controls. Cocaine dependent and healthy control subjects (n = 11 per group; ages 32 ± 7 vs. 32 ± 8 yr.) were injected with 10 mCi [^{123}I]β-CIT and imaged 24-30 hr later under sustained equilibrium conditions. The ratio of specific to non-displaceable brain uptake (V3" = [striatal - occipital]/occipital), a measure proportional to the binding potential (B_{max}/K_D) was used as an outcome measure. Results showed significant elevations (mean 22 ± 29%; range -26 to +56%) in striatal V3" values in acutely abstinent cocaine subjects compared to age- gender-, and ethnically-matched controls (10.6 ± 2.7 vs. 8.8 ± 1.8; p = 0.04, two-tailed paired t-test). These results are consistent with post-mortem findings of elevated DAT number (Bmax) in cocaine overdose victims.

Based on these findings, we have since sought to clarify whether these changes in DAT would persist with sustained abstinence from cocaine. Sixteen cocaine abusers (mean + SD age = 31 ± 6 yr.; 5 F, 11 M) were studied during periods of acute (< 72 hr) and sustained (2-4 weeks) drug abstinence. Subjects were injected with 10 mCi of [^{123}I]β-CIT and imaged at 24 hr post-injection under sustained equilibrium conditions. The specific to nonspecific equilibrium partition coefficient (V3" = (striatum - occipital) / occipital), a measure proportional the binding potential (Bmax/KD), was used for all comparisons. No significant within-subject differences in V3" values were observed over time (week 0 = 10.3 ± 2.2, n = 16: week 2 = 9.8 ± 2.7, n = 12; week 4 = 9.0 + 2.0, n = 12; Effect of Week, p = 0.36 - 0.96, repeated measures ANOVA). Within subject comparisons of initial (week 0) and final (week 2 or 4) V3" values were similarly negative (10.3 ± 2.2 vs. 9.7 ± 2.2, n = 16; mean = 0.7 ± 2.1; p = 0.24, paired t test). Nevertheless, elevations in V3" decreased in their level of statistical significance over time (p = 0.002, 0.07, and 0.18, respectively) relative to healthy controls (V3" = 8.2 ± 1.5; n = 23). Dopamine transporter binding appears to remain elevated in chronic cocaine abusers during early periods (i.e. 2 - 4 weeks) of sustained drug abstinence. In remains a possibility that DAT elevations may only gradually normalize with more prolonged drug-free intervals (i.e. > 4 weeks).

Jon Kar Zubieta - Dopamine and Opioid Alterations in Human Cocaine Abusers: PET Studies. It is well accepted that the behavioral actions of cocaine are mediated through the dopaminergic system. In addition, opioid systems also may play a role in its reinforcing actions. For example, in experimental animals the opioid antagonist naloxone attenuates the reinforcing and locomotor effects of acute cocaine administration; short-term cocaine administration increases both enkephalin and dynorphin mRNA; chronic "binge pattern" treatment with cocaine in experimental animals has been observed to elicit increases in μ and κ opioid receptor densities in a number of brain regions. Mu opioid receptor binding in chronic cocaine abusers was examined *in vivo* , using [^{11}C] carfentanil (CFN) and PET, shortly after withdrawal and again after 4 weeks of supervised abstinence.

Ten male cocaine abusers (age 32 ± 4 yrs, mean ± SD.) and seven age- and sex-matched controls (age 32 ± 6 yrs) were scanned with a GE 4096 PET camera after i.v. administration of 20 ± 2 mCi [^{11}C]CFN. Cocaine abusers were studied twice: after chronic use, 1-4 days after last cocaine binge, and again after 4 weeks of withdrawal in a closed unit Specific [^{11}C]CFN binding was significantly increased (range 25-52%) in caudate, thalamus and neocortical regions of the cocaine addicts compared with healthy controls (unpaired, two-tailed t-test, $p > 0.05$). Self-rated cocaine craving was significantly correlated with μ-opioid binding in amygdala, anterior cingulate, frontal and temporal cortex ($r=0.63$, 0.71, 0.72, 0.73, respectively, $p < 0.05$). Mu receptor availability was also associated with the recent use of cocaine: μ receptor binding correlated negatively with urine levels of the cocaine metabolite benzoylecgonine in multiple brain regions (range of correlations, $r = -0.52$ to -0.83). The upregulation of μ receptors persisted after 4 weeks of withdrawal. These data suggest that chronic cocaine abuse is associated with increase μ-opioid receptor binding, which correlates with the intensity of cocaine craving and persists even after prolonged withdrawal. Recent cocaine use also appears to be associated with increased release of endogenous opioid and increased receptor occupancy. The results demonstrate the involvement of the opioid system in cocaine addiction. In this regard, μ-opioid receptors appear to be associated with the experience of craving for cocaine in humans, after acute withdrawal of the drug. Further studies are necessary to explore the involvement of the opioid receptor sites in cocaine addiction, and the clinical significance of these interactions.

Stephen Dewey - Opioid and GABAergic Modulation of Dopamine Release: PET and In Vivo Microdialysis Studies. Positron emission tomography (PET) has been shown to be useful for non-invasively measuring interactions between functionally-linked neurotransmitter systems in the human and primate CNS. Studies in our laboratory continue to focus on the application of this technique to questions of clinical relevance, including cocaine abuse. While recent work from our laboratory and others has been targeted at the development of new drugs that effectively compete with cocaine at the dopamine transporter (DAT), we have taken a different approach based upon our PET findings with the neurotransmitter interaction paradigm. Rather than administer drugs that directly compete with cocaine at the DAT, we have examined the effects of drugs (ethanol and various GABAergic and opioid drugs) that potentiate other dopamine-inhibiting neurotransmitters on cocaine-induced dopamine release. Our data demonstrates that naloxone, Gamma-vinyl GAB A (GVG, a selective inhibitor of GABA-transaminase), and lorazepam, dose dependently attenuate cocaine's ability to increase extracellular dopamine and gross locomotor activity. Furthermore, these data demonstrate that while sedative hypnotic drugs working on the GABAergic system (*i.e.,* ethanol and lorazepam) clearly attenuate cocaine-induced dopamine release in the nucleus accumbens, the sedative and addictive properties of these drugs limit their utility as effective treatments for cocaine abuse. The GABA-transaminase inhibitor GVG, however, exerts its effects by directly inhibiting the catabolism of synaptic GABA thereby effectively increasing GABAergic tone. Due to this specificity, the side effects, such as sedation, which are associated with drugs that augment binding of the GABA-receptor complex are not observed. Furthermore, GVG is not an addictive drug. Thus by specifically increasing the concentration of the naturally occurring neurotransmitter, rather than potentiating neurotransmission, GVG offers a unique strategy for potentially treating the neurochemical consequences of cocaine abuse with a minimum of side effects. These findings support further investigation into the use of this unique strategy for attenuating increases in extracellular dopamine concentrations following cocaine administration. Current studies investigating the ability of these drugs to attenuate cocaine self-administration are ongoing as well. This research was carried out at Brookhaven National Laboratory under contract DE-AC02-76CH00016 with the U. S. Department of Energy and supported by its Office of Health and Environmental Research and supported by the National Institutes of Mental Health (MH-49165) and NARSAD.

Michael H. Baumann - Neuroendocrine Responsiveness to Serotonergic Drug Challenge During Cocaine Withdrawal. Increasing preclinical evidence indicates that chronic cocaine alters central serotonin (5-HT) function. For example, several investigators have shown that neuroendocrine effects elicited by 5-HT releasing agents (i.e. fenfluramine) are blunted in rats withdrawn from repeated cocaine injections. Such findings are intriguing because (1) withdrawal from binge cocaine use in human is accompanied by symptoms that resemble major depression and (2) abnormalities in 5-HT transmission are implicated in the pathophysiology of depression. In the present work, we used a neuroendocrine challenge approach to evaluate 5-HT responsiveness in human subjects who self-administered intranasal cocaine in an in-patient research setting. Male poly-substance abusers (n = 8) participated in two daily self-administration sessions for 5 consecutive days. At each session subjects snorted either cocaine (96 mg cocaine) or placebo (4 mg cocaine), with cocaine being presented in a double-blind randomized fashion at one of the daily sessions. Cortisol and prolactin responses to cocaine or placebo were assessed on days 1 and 5 of the self-administration sessions. Subjects were challenged

with fenfluramine (80 mg, p.o.) to assess 5-HT responsiveness 5 days before and 3 days after the cocaine treatment regimen. Intranasal cocaine increased cortisol, but did not affect prolactin, on days 1 and 5. Fenfluramine significantly elevated both cortisol ($p < 0.01$) and prolactin ($p > 0.0001$) prior to cocaine exposure. Interestingly, the fenfluramine-induced cortisol response was significantly reduced ($p < 0.05$) after repeated cocaine self-administration. The present results provide support for the notion that withdrawal from chronic cocaine causes 5-HT dysfunction in human drug addicts. Although these data must be regarded as preliminary, the assessment of 5-HT function in human cocaine users deserves further study. Determining the neurobiological substrates of cocaine withdrawal may aid in the development of more effective treatment strategies for cocaine dependence.

Julie K. Staley - Regulatory Alterations in the Molecular Signature of the Dopamine Synapse in Cocaine Overdose Victims. Dade County, Florida serves as a gateway for the importation of cocaine into the United States from source nations in South America. The large quantities of cocaine transiting through Miami has resulted in one of the largest cocaine-epidemics in history exemplified by the high incidence of cocaine fatalities Approximately 10% of all cocaine overdose (CO) cases present with the excited delirium (ED) syndrome which is characterized by hyperthermia, paranoia, agitation, bizarre and violent behavior. Radioligand binding and autoradiography methods were used to identify neuroadaptative changes in pre- and postsynaptic dopaminergic (DAergic) markers in neuropathological tissue specimens from CO and ED victims. Quantitative *in vitro* autoradiography using the radiolabeled analogs of cocaine, [^{125}I]RTI-55 and [^{3}H]WIN 35,428 demonstrated a 2-fold elevation in the apparent density of DA transporters throughout the striatum in CO victims, but not ED victims as compared to drug-free and age-matched control subjects. Saturation binding analysis of [^{3}H]WIN 35,428 binding to putamen membranes demonstrated that in the CO victims, the number of high affinity cocaine recognition sites was increased 5-fold , while the density of low affinity cocaine recognition sites was not changed. Conversely, in the ED victims, the density of high affinity cocaine recognition site was not changed, while the number of low affinity cocaine recognition sites was decreased 2-fold as compared to the control group. The density of [^{125}I]iodovinyltetrabenazine binding to the neuronal vesicular monoamine transporter was not different across cocaine overdose subgroups as compared to drug-free and age-matched control subjects. The density of D_1 receptors measured using [^{3}H] SCH 23390 was decreased 2-fold throughout the striatal reward centers of both CO and ED victims as compared to the control group. No alteration in [^{3}H]raclopride binding to D_2 receptors was seen in the DA-rich sectors of the striatum across groups. The density of D_3 receptors measured using [^{3}H]-(+)-7-OH DPAT in the presence of GTP was markedly elevated (2-3-fold) over the limbic sectors of the striatum in the CO victims but not the ED victims as compared to drug-free and age-matched control subjects. Interestingly, in the anterior hypothalamic nuclei of the ED cases, D_2 receptor densities were markedly reduced, while D_1 receptor number remained unaltered as compared to drug-free and age-matched control subjects.

Since cocaine blocks the reuptake of DA, the increase in the apparent density of high affinity cocaine recognition sites on the DA transporter may reflect an increase in DA transport as an acute compensatory response to the elevated synaptic levels of DA. The lack of a compensatory increase in the high affinity cocaine recognition site in the ED subgroup may result in elevated synaptic levels of DA following a cocaine "binge" that may lead to the psychosis and paranoia associated with this syndrome. The lack of a change in the density vesicular monoamine transporters in the striatum suggests that DA nerve terminal integrity remains intact after chronic cocaine abuse. The long-lasting elevations in synaptic DA levels that result from the blockade of DA reuptake result in regulatory adaptations in pre- and postsynaptic DA receptor numbers which may underlie the behavioral and physiological effects of cocaine. Decreased D_1 receptor number may represent agonist (DA)-induced down-regulation of the receptors and may mediate tolerance to cocaine's euphoriant effects. The neuroadaptive increase in D_3 receptor density in the brain reward circuits suggests that regulatory alterations in D_3 receptor number may, in part contribute to the reinforcing effects of cocaine that lead to drug craving and relapse. The selective down-regulation of the D_2-like receptors in the anterior hypothalamic nuclei in the ED victims may contribute to the hyperthermia associated with excited delirium and sudden death. Hypothalamic D_2-like receptors mediate decreases in core body temperature, while D_1 receptors mediate the opposing increase in core body temperature. The decreased number of D_2 receptors may promote hypertheimia via a D_1 -mediated rise in core body temperature that is unopposed by a D_2-mediated feedback regulation. These regulatory adaptations in the DA synaptic markers may contribute to the development of cocaine dependence, and the adverse behavioral sequelae associated with chronic cocaine abuse. Supported by DA 06227 and DA 09494.

ANTIBODY- AND PROTEIN-BASED THERAPIES FOR DRUG ABUSE

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Symposium overview. Abuse of psychoactive chemicals can result in neurotoxic effects that are difficult to treat medically. Successful therapy is often hindered by the lack of useful antagonists for many of these chemicals and by the extensive distribution of these chemicals out of the blood stream. Recent advances in immunotherapy and protein-based therapies suggest these novel approaches could be beneficial in the treatment of drug abuse.

P. R. Pentel: ANTIBODY ENGINEERING FOR THERAPEUTIC APPLICATIONS

Drug-specific antibodies, which bind drugs with high affinity and specificity, are of interest as novel therapies for drug abuse. Drug-specific antibodies bind and inactivate drug in serum, and reduce drug distribution to target tissues. When administered to animals after an overdose, drug-specific antibodies can redistribute drug out of tissues and rapidly reverse toxicity. Although the large amounts of antibody needed to accomplish this may themselves be toxic, the use of enzymatically produced antibody Fab fragments, genetically engineered Fv fragments, or small peptides that mimic the antibody binding pocket offer means of rationally designing agents that are less toxic, more effective, and have suitable pharmacokinetic properties.

Drug-binding antibodies may also be useful in the treatment of chronic drug abuse. In animals immunized against drugs such as heroin or cocaine, drug distribution to the brain is reduced, as is drug effect. The total amount of drug-specific antibody present in an immunized animal is small compared to the typical molar dose of an abused drug; whether the beneficial effect of immunization is surmountable by repeated dosing or increasing the drug dose is not yet clear.

Catalytic antibodies can be produced that mimic the actions of drug metabolizing enzymes, and thereby enhance drug clearance. Because drugs that are smoked or administered i.v. reach the brain within minutes, the activity of catalytic antibodies will have to be very high in order to appreciably alter drug effect and not be surmountable by increasing the drug dose. Novel strategies will be needed to produce such high activity catalytic antibodies.

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J. R. Cashman: COCAINE CATALYTIC ANTIBODIES

Cocaine abuse is implicated in more medical complications and deaths that any other prohibited chemical agent. For example, cocaine overuse is associated with more emergency department visits and more deaths than any other drug of abuse. It is apparent that cocaine use among polydrug abusers, presumably occurring at ever higher doses via intravenous injection or by smoking, constitutes an increasingly more toxic situation. New strategies for preventing the toxicity and abuse of cocaine are needed and novel approaches employing modem molecular biology techniques are required to develop treatment for cocaine overdose. The approach presented here is the use of catalytic antibodies in the creation of selective binding agents and detoxification catalysts for use in the emergency room setting under the direction of a physician. The central hypothesis of the work is that a "transition state mimic" hapten of cocaine hydrolysis can elicit an immune response that affords anti-cocaine catalytic esterolytic activity. Procurement of a highly catalytically active monoclonal antibody will provide a means to determine the sequence of an animal's anti-cocaine catalytic antibody. Current advances in

humanization of catalytic antibodies could then be used to humanize a cocaine hydrolytic detoxification catalysts. The net result is to design and develop a cocaine detoxification catalyst by using biochemical principles. The procurement of anti-cocaine catalytic antibodies provides an opportunity to develop fundamental applications in molecular biology of direct relevance to drugs of abuse research that may be of benefit in treating human cocaine toxicity.

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K. D. Janda: ACTIVE IMMUNIZATION SUPPRESSES PSYCHOACTIVE EFFECTS OF COCAINE

Cocaine is a powerful addictive substance and new strategies are needed to treat its abuse. Despite intensive efforts, there are no proven medications for treatment of cocaine craving and addiction. Immunopharmacotherapy offers an alternative for addressing the cocaine problem. Early work demonstrated that antibodies specific for certain drugs were useful in the attenuation of their effects. It has also been shown that catalytic antibodies could degrade cocaine *in vitro* but the rates of the reaction must be improved to be of practical value. Perhaps the ultimate goal in an immunological approach aimed at the abatement of cocaine abuse is the *de novo* design of a vaccine. Recently, we took steps in this direction bringing together immunochemist and a well-defined behavioral model and demonstrated the suppression of the psychoactive effects of cocaine. In this context, the design and synthesis of two stable cocaine conjugates were discussed. Active immunization with these antigens was able to suppress the locomotor activity and stereotyped behavior in rats administered cocaine. In addition, this protocol has been examined as a potential treatment in cocaine relapse prevention. These studies suggest that immunopharmacotherapy offers a non-toxic, substance-specific strategy that should not affect the normal neurochemical physiology.

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S. M. Owens: IMMUNOTHERAPY FOR PHENCYCLIDINE ABUSE

Abuse of psychoactive chemicals like phencyclidine (PCP) can result in neurotoxic effects that are difficult to treat medically. Successful therapy is often hindered by the lack of useful antagonists for many of these chemicals and by the extensive distribution of these chemicals out of the blood stream. As a possible solution, immunotherapy for PCP abuse was evaluated using high affinity anti-PCP monoclonal antibody fragments (anti-PCP Fab). The effectiveness of the therapy was evaluated through an extensive series of interrelated pharmacokinetic, behavioral and tissue distribution studies in a rat model of PCP overdose. The pharmacokinetic studies showed that when anti-PCP Fab is administered after PCP is fully distributed in the rats, it can quickly bind the drug and radically decrease the volume of distribution of the highly lipophilic PCP. In behavioral studies, the anti-PCP Fab rapidly reverses PCP-induced behavioral effects and ataxia. Indeed, the animals appear to return to normal behavior within 10 min of treatment. In studies of PCP tissue distribution after anti-PCP Fab treatment, the anti-PCP Fab decreased PCP concentrations in the brain by 90% within 10 min of treatment. These findings suggest a promising role for immunotherapy in the treatment of central nervous system-mediated chemical toxicity and drug abuse in humans.

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PREVALENCE, PROJECTIONS AND POLICY

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BUILDING A POLICY RELEVANT DRUG INDICATOR SYSTEM

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For more than 20 years, various Federal agencies in law enforcement, health, and other fields have sponsored data collection efforts that produce indicators of the nation's alcohol and other drug abuse problems. While these data collection efforts have generated a considerable amount of information, there has been little coordination among agencies, and thus the data overlap in some cases and in others have failed to capture information on important subpopulations and important aspects of drug related harm. In addition, different and seemingly inconsistent findings can be inferred from these data because the various indicator systems were designed for different purposes, focus on different populations, and often use different measures of drug abuse problems.

The need to adapt and modify existing data systems to meet new demands has heightened over the past several years as Congress, Federal agencies, and State legislatures around the country have called for greater rationality in the allocation of resources and greater accountability in the expenditure of public dollars for alcohol and other drug intervention programs. These mandates have also begun to shift the emphasis on data development away from prevalence indicators toward indicators of need for treatment and outcomes of interventions. Ever more systems are being added.

The purposes of the current research are 1) to analyze both the problems and untapped potential for existing data to be used more creatively in exploring drug policy issues; and 2) to suggest guidelines and a conceptual framework for identifying and evaluating data needs and analyses that will effectively support substance abuse policy at the Federal, State and local level. We recommend that data needs be explored within a systems perspective and conclude by listing key challenges and opportunities facing those charged with developing drug indicators.

REFERENCES

Ebener, P.; Caulkins, J.; Geschwind, S.; McCaffrey, D. and H. Saner. Improving Data and Analysis to Support National Drug Abuse Policy Santa Monica, CA., RAND, 1994

DIFFICULTIES IN MATCHING POLICIES TO THE EPIDEMIC CYCLE: THE CURRENT HEROIN UPSWING

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The popularity of abusable psychoactives follows a somewhat predictable cyclic pattern: introduction, rapid spread, narrowing and deepening of the market, decline, quiescence, reintroduction. An ideal set of policies would be matched to phases, of the epidemic cycle. Policies directed at reducing initiation, such as enforcement and the distribution of primary prevention messages through the schools and in the mass communications media, ought to be concentrated in drugs whose rates of initiation are rising, while treatment efforts should be heaviest once a drug is past its peak. Secondary and tertiary prevention, and harm-reduction education, ought to be concentrated near the peaks in initiation.

Implementing such an ideal prescription runs into two distinct kinds of difficulties: problems of institutional management and problems of prediction. Resources are hard to move from drug to drug or from activity to activity, and drug trends are hard to spot, at least in part because existing data collection and analysis efforts produce largely lagging, rather than leading or coincident, indicators of initiation rates.

Heroin provides an illustration. The price of heroin, adjusted for purity and inflation, has fallen by almost an order of magnitude over the past decade; in some cities, it is cheaper per intoxicated hour than cocaine or beer. Higher purity and lower price make smoking and snorting technically and economically feasible for many users for whom fear of injection once constituted a high barrier to heroin initiation. Enforcement officials report major increases in retail-level heroin distribution, with many crack dealers beginning to carry heroin as a second product. References to heroin permeate popular culture, and there are widespread anecdotal reports of increased use of the drug in social milieux where it had been vanishingly rare. Yet none of the conventional drug abuse data systems -- the two national surveys, DAWN, or DUF -- provides any solid support for the notion that heroin use has been rising.

There are two separate explanations for this apparent paradox. First, national indicators tend to mask highly localized phenomena. Second, rising purity and falling price tend to decrease the rate of adverse consequences among existing heavy users, and thus offset any increases in arrests or emergency room visits or deaths caused by increasing prevalence. Improving data collection and analysis could provide better leading-indicator data. But identifying trends will remain difficult. The resulting uncertainty puts a premium on interventions worth implementing when the probability of a major upswing is far from unity.

MODELING THE OPTIMAL MIX OF PUNISHMENT AND TREATMENT FOR DRUG CONTROL

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Treatment of heavy cocaine users is many times more cost-effective in reducing cocaine consumption than the best supply-control program, given the current allocation of funds across program types, and could cut United States consumption by as much as a third if extended to all heavy users. These findings are documented in Rydell and Everingham, 1994.

The study compares four methods of reducing cocaine consumption in the United States. The first three (source country control, interdiction, and domestic enforcement) are supply-control programs that reduce consumption indirectly by punishing drug suppliers, thereby causing the retail price of cocaine to increase, and hence causing drug use to decrease. The fourth (treatment) reduces consumption directly by decreasing the number of drug users. Source country programs eradicate coca leaf and seizes coca base, cocaine paste, and the final cocaine product in the producing nations (primarily Peru, Bolivia, and Columbia). Interdiction by the U.S. Customs Service, Coast Guard, Army, and Immigration and Naturalization Service seizes both cocaine and drug-trafficker assets before the contraband enters the United States. Domestic enforcement by Federal, State, and local law enforcement agencies seizes cocaine and assets and imprisons drug dealers and their agents. Treatment of heavy drug users includes both outpatient and residential programs.

Evaluating these alternative control programs requires comparing their effects as well as their costs. But supply-control and treatment programs produce different kinds of immediate results. This research compares them by identifying a common measure - the annual program cost required to reduce U.S. consumption of cocaine by a given amount. The lower the cost, the more cost effective the program. The research shows that treatment of heavy users outperforms all three supply-control programs. The specific estimates in the study are that U.S. cocaine consumption can be reduced by one percent by spending an additional $34 million per year on treatment. To achieve the same effect we would have to spend annually an additional $250 million for domestic law enforcement against drug dealers, or $370 million for interdicting the drug at our borders, or $780 million to help foreign governments cut supplies at the source. This does not, however, mean that all

money now spent on supply control could more effectively be spent on treatment. There are limits to how many heavy users can be induced to undergo treatment and how often they can be induced to do so. If all heavy users could be treated once each year (which is unlikely), the average reduction in cocaine consumption over the next 15 years would be about one-third. The cost of this expansion in treatment would be about one-fourth of the current supply-control budget. Thus, this research by no means suggests that deep cuts in supply-control are advisable. However, it does suggest that, at the margin, money available for cocaine control would be better spent on expanding treatment of heavy users than on extending supply-control programs.

REFERENCES

Rydell, C. P. and Everingham, S. Controlling Cocaine: Supply Versus Demand Programs. Santa Monica: RAND, 1994.

ASSESSING THE EQUITY OF THE SUBSTANCE ABUSE AND MENTAL HEALTH BLOCK GRANT FORMULA

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With Congress shifting to block grants as the principal means for distributing federal moneys to the states, the question of how equitably the distribution formulae allocate will come into sharper focus. Burnam *et al.,* 1996 examined the formula for distribution of the Substance Abuse (SA) and Mental Health (MH) block grant (involving approxiamately $1.2 billion in FY95), which has been the subject of considerable discussion and amendment over the last 15 years. The SAMH formula is a relatively sophisticated by current federal standards; it incorporates more variables and has a more explicit research and analytic base than many other BG formulae. Nonetheless it probably substantially fails to accomplish its goals, for both conceptual and empirical reasons.

Conceptually, the formula is flawed in ways that may lead it to exacerbate rather than ameliorate differences among states, because it ignores three factors: (1) The federal government's distribution of other money for both substance abuse and mental health; (2) The distribution of private insurance funding for the same services; and (3), the fact that the funding goes almost exclusively to services for the poor. The implementation problems are also serious and illustrate nicely the empirical problems faced by such formulae. (1) Data are simply not available on the population distribution of some of the problems targeted (*e.g.* serious emotional disorders among adolescents). (2) The formula incorporates incomplete analysis of dated data series. (3) Some series critical to the formula are available only with a long lag, so that annual distributions are likely to be judged, retrospectively, as inequitable. (4) Multiple targets are awkwardly handled within a single formula.

The SAMH allocation formula has been a moving target, driven in large part by increasing sophistication of relevant data and analysis that has exposed the weaknesses of whatever is the current formula. The fact that some state always, correctly, believes that a revision of the formula to incorporate newer findings would be to its advantage is probably the essential instigating process. Underlying this is also the problem that there is no "correct" allocation formula. It must reflect changing views about equity and knowledge of the beneficiary populations. Our continuing investment in data and research on substance abuse and mental health is arguably a major factor in the instability of the formula; that is not an argument against such investments (which are modest enough) but an appreciation of yet another unintended consequence.

REFERENCES

Burnam, M. A.; Reuter, P.; Adams, J.; Palmer, A.; Model, K.; Heilbrunn, J.; Marshall, G.; McCaffrey, D.; Wenzel, S. and R. Kessler Review and Evaluation of the Substance Abuse and Mental Health Services Block Grant Forrmula Santa Monica, CA., RAND 1996

BEHAVIORAL AND PHARMACOLOGICAL INTERVENTIONS FOR PREGNANT SUBSTANCE ABUSERS **L. *Amass*[1], *R. Elk*[2], *D. Svikis*[3], *S. Schnoll*[4], *R.E. Johnson*[3] & *L.P. Finnegan*[5] University of Toronto[1], University of Texas HSC at Houston[2], Johns Hopkins University School of Medicine[3], Virginia Commonwealth University[4], & National Institutes of Health[5]**

Drugs and alcohol use during pregnancy increases obstetrical complications, poses significant maternal and fetal health risks and is a prevalent problem in drug abuse treatment. As reviewed below, behavioral and pharmacological interventions can help reduce drug and alcohol use during pregnancy and improve outcomes for drug-dependent pregnant women and their children.

CONTINGENCY MANAGEMENT INTERVENTIONS IN THE TREATMENT OF COCAINE-DEPENDENT PREGNANT WOMEN ***R. Elk.*** This study determined whether contingency management interventions (CMI), as adjuncts to a behaviorally-based gender-sensitive treatment, would improve outcomes in cocaine-dependent pregnant women. **Methods.** Cocaine-dependent pregnant women were randomly assigned to one of 3 treatment groups: Group A: Baseline Treatment + CMI for cocaine abstinence [$18 for each cocaine-free UA, and an additional reinforcer [$20] if all 3 UAs required per week were cocaine-free]; Group B: Baseline Treatment + CMI for cocaine decrease and abstinence [$12 for each UA with a decrease in cocaine-metabolite; $18 for each cocaine-free UA, and an additional reinforcer [$20] if all 3 UAs required per week decreased in cocaine or were cocaine-free.]. Group C: Baseline Treatment alone (Control group). **Results.** Treatment Retention: Significantly more patients in the 2 CMI groups completed treatment (69%) compared with those in the control group (31%) [p=0.027]. Compliance with Prenatal Care: There was a very high rate of compliance with prenatal care (75%) across all groups. Compliance with prenatal care was associated with retention in treatment. Among patients who completed treatment, there was a significantly higher rate of compliance in the 2 contingent groups than in the control group [p=0.067]. Cocaine Abstinence During Treatment: There was a higher rate of cocaine abstinence in Group A, although this abstinence rate did not reach statistical significance. There was also a higher rate of abstinence from cocaine in patients who remained in treatment. Cocaine Abstinence at delivery: A higher proportion of patients in Group A were cocaine free at birth (75%) compared with patients in the other two groups (45% abstinent). Perinatal Outcome: Significantly more patients in Group A (75%) had none of 4 risk factors [preterm delivery, low birth weight, preterm labor, premature rupture of membranes] compared with 27% of patients in the other 2 group [p=0.09]. **Conclusion.** Adjunctive CMIs arc effective in enhancing treatment retention and compliance with prenatal care, initiating cocaine abstinence, and improving rates of perinatal outcome. These behavioral treatments can be adapted to, and are effective in, the treatment of pregnant cocaine-dependent women.

EFFECTIVENESS OF BEHAVIORAL INCENTIVES FOR MOTIVATING TREATMENT PARTICIPATION IN PREGNANT DRUG ABUSING WOMEN ***D. Svikis, N. Haug, and M. Stitzer.*** The Center for Addiction and Pregnancy (CAP) is an interdisciplinary "one stop shopping" program proving drug treatment, OB/Gyn care, and pediatric services at a single site. Nonetheless, many pregnant women discontinue treatment prematurely with the highest rates of drop out occuring upon transfer from residential to intensive day treatment. This study determined whether behavioral incentives improve patient participation and treatment retention during the first seven days after transfer from residential to outpatient care. **Methods.** Women were primarily opioid- (80%) and/or cocaine- (84%) dependent. Over half (58%) of opioid-dependent women qualified for and elected to receive methadone maintenance as a therapeutic adjunct. Subjects were randomly assigned to one of four incentive conditions: $0 (standard care); $1 per day; $5 per day or $10 per day. Vouchers were earned each day the subject attended at least four hours of treatment programming and were dispensed in the form of gift certificates. **Results.** The impact of voucher incentives on treatment participation and retention were examined separately for methadone-maintained (N=66) and non-methadone maintained (N=76) women. During the incentive week: 1) methadone-maintained subjects attended significantly more full treatment days (5.2) than non-methadone maintained subjects (2.8);2) due to high base rates of program attendance, voucher incentives had no effect on treatment participation for methadone-maintained subjects; and 3) for non-methadone maintained subjects, higher magnitude incentives ($5/10) had a modest effect on treatment participation and retention relative to low magnitude incentives ($0/$1) (3.3 versus 2.3 full days attended during the incentive week). **Conclusion.** The present study confirmed that methadone

maintenance is a powerful therapeutic adjunct which is associated with significantly better treatment participation and retention. The study also found that behavioral incentives can facilitate treatment participation and retention for abstinence-based patients.

FINANCING VOUCHER PROGRAMS FOR PREGNANT SUBSTANCE ABUSERS THROUGH COMMUNITY DONATIONS ***L. Amass.*** A promising contingency management approach is to create a voucher-based economy in which patients earn vouchers contingent on drug-free urines that they can exchange for goods and services. However, a drawback of voucher programs is their cost. This presentation discussed the fund raising techniques for, feasibility of, and cost-benefits of establishing a community-sponsored on-site voucher exchange for use in a contingency management program for pregnant drug users (The Pregnant and Clean Project or Project PAC). In Project PAC, pregnant patients receive vouchers contingent on the demonstration of drug abstinence by urinalysis. Vouchers are redeemable at an on-site exchange containing a variety of products and services. The on-site exchange is unique because it is funded and stocked entirely by community donations. **Methods.** A direct mail fund raising campaign was used to solicit donations from 198 corporations, manufacturers and local retailers. In addition, local volunteers were solicited through posters, word-of-mouth and electronic mail advertising. Components of the campaign included selecting goods and serviced to stock in the voucher store, identifying and targeting potential sources of community sponsorship, constructing an effective donation request package, and carefully planning follow-up to our direct mail. Seven categories of goods and services were targeted for donations: baby accessories, baby clothes, toys, maternity wear/products, diapers, entertainment/recreation and equipment. Active fund raising occurred during a 2-month period. **Results.** The positive response rate obtained over the next 8-months for corporate sponsorship was 19%. The following groups comprised our positive respondents: 53% were manufacturers, 34% were local attractions/restaurants and 13% were local retailers. In addition, 120 women volunteered to produce and donate hand-made baby and maternity items. The total retail value of all goods and services donated to the program (including taxes) totaled approximately US$8,000. Goods were donated to the 7 categories (based on their dollar value) in the following percentages: 49% to entertainment/recreation, 19% to toys, 13% to baby clothes, 9% to maternity wear/products, 4% to equipment, 3% to baby accessories and 3% to diapers. **Conclusion.** These data demonstrate the feasibility of community-sponsored voucher programs. Such community sponsorship may offer a cost effective alternative for financing voucher programs for substance abuse treatment and ultimately increase their use and acceptance by the general treatment community.

CHEMOTHERAPY FOR THE TREATMENT OF ADDICTION DURING PREGNANCY ***S. H. Schnoll.*** Methadone is the only drug available for pharmacotherapy of pregnant opioid-dependent women and has been used for over 25 years. However, there is a paucity of literature regarding the intrapartum use of methadone and its effects on pregnancy and fetal well being. Animal studies of opioid exposure in pregnancy demonstrate that rapid cycling between intoxication and withdrawal has adverse consequences on fetal development and can lead to fetal demise. These studies support the clinical use of long-acting opioids to stabilize the fetus. However, numerous studies show that prenatal exposure to drugs in animals results in alterations in brain chemistry and physiology. The significance of this for humans is currently unknown. Human studies are quite limited. Research has demonstrated that methadone metabolism is accelerated during the third trimester of pregnancy. To compensate for this change in metabolism, the dose of methadone may need to be increased during this period. However, subsequent studies have demonstrated that splitting the dose of methadone may provide more consistent blood levels. The effect of maternal methadone on neonatal withdrawal is still not well understood. Lower doses of methadone must be tempered with the potential increase in illicit drug use and involvement of other behaviors that could be risky for the mother and fetus. Despite this long history of methadone use, little information is available on the determination of the initial dose to be utilized in a pregnant woman and how to adjust the dose to assure the best outcome. In addition, little information is available regarding the metabolism of methadone during the first and second trimesters and precisely when the metabolic changes occur that may require alterations in dosing schedules. Given the lack of studies on the intrapartum effects of methadone and pregnancy and the recent availability of new drugs to treat opioid dependence, it is imperative to begin to carefully study methadone in pregnant women so that comparisons can be made with the efficacy of newly available drugs to determine which would be best for the treatment of opioid dependence during pregnancy.

USE OF BUPRENORPHINE IN PREGNANT OPIOID-DEPENDENT PATIENTS

R. E. Johnson, D. Jasinski, and D. Svikis. Five to 10 thousand infants are born annually to opiate-dependent mothers. Neonates of heroin-dependent and methadone-maintained mothers generally exhibit significant abstinence syndromes following birth and often require intensive and extended medical treatment when compared to non-drug exposed infants. The neonatal withdrawal syndrome from methadone is reported to be more severe than that from heroin. The severity of withdrawal from methadone has been reported by some to be dose related. Others have found no dose relationship. Reduction or elimination of the neonatal opiate withdrawal syndrome would reduce: 1) emotional and physiologic stress in the neonate and 2) health care costs. Several laboratory studies report little or no autonomic signs and symptoms of withdrawal following the abrupt termination of chronically administered buprenorphine in adults. In premature neonates (27-32 weeks), buprenorphine is reported to be safe but possibly less effective than other opiates in producing analgesia and sedation. It has also been reported that four females maintained on buprenorphine throughout their pregnancy had normal pregnancies and deliveries with no or minimal withdrawal observed in the neonates. However, no systematic studies have been conducted to assess the safety of buprenorphine in pregnant females at dose levels (4-16 mg sublingual) studied in clinical trials assessing buprenorphine maintenance therapy. We hypothesize that: 1) buprenorphine is safe for both the pregnant opiate-dependent female and fetus, and 2) the buprenorphine exposed neonate will experience a shorter and milder withdrawal syndrome than observed with methadone. We are currently screening potential patients to participate in a study is to assess the safety of buprenorphine in the pregnant opiate-dependent woman and fetus during weeks 24-42 of gestation and to evaluate the neonate for opiate withdrawal symptoms following delivery. Maternal and neonatal safety outcome measures will be evaluated during the antepartum, labor/delivery, and post partum periods. Additional outcome measures include: neonatal withdrawal symptomotology, medications to treat the neonatal abstinence syndrome, and maternal and neonatal pharmacokinetic parameters. A randomized, double-blind clinical trial comparing buprenorphine to methadone will follow the safety study.

DISCUSSION ***L. P. Finnegan.*** The NIH and FDA recognize the need to research interventions catering to the special needs of women. Programs with the potential to enhance recovery and reduce recidivism in pregnant substance abusers are needed. Dr. Elk's and Svikis's comprehensive programs for drug-dependent pregnant women highlight the need to provide an array of services at one site. Dr. Elk demonstrated that adding a contingency management intervention improves treatment retention, abstinence and perinatal outcome. Conducting a cost-benefit evaluation of this intervention is an important and exciting area for future research. Dr. Svikis investigated the effectiveness of behavioral incentives for motivating treatment participation and retention. Vouchers enhanced retention more effectively for abstinence-based as opposed to methadone-maintained patients, underscoring methadone's usefulness in retaining patients in treatment. Larger magnitude incentives also promoted better retention. The above two studies demonstrate that behavioral interventions improve outcomes and are useful adjuncts in the treatment of pregnant drug-dependent women. Dr. Amass' pursuit of techniques for reducing the cost of voucher programs, and the establishment of a community-sponsored, on-site voucher exchange is extremely innovative. The categories of donations targeted were clearly gender specific and moreover, specific to women in the perinatal period. Since funding for substance abuse services has always been limited, community sponsorship is an excellent way to provide contingency management interventions in a non-cost prohibitive fashion. This creative approach should be replicated in other communities. Dr. Schnoll gave an excellent overview on methadone treatment during pregnancy, clearly illustrating that the benefits of providing methadone during pregnancy override the risk of neonatal abstinence. Studies on methadone withdrawal and blood levels in pregnant women would also benefit from concurrent biophysical evaluations and more research on methadone dosing during pregnancy is needed. Finally, the opportunity to explore the benefits of new medications is exciting. Dr. Johnson's systematic approach for studying buprenorphine will provide considerable information about its safety for both the mother and the fetus. Buprenorphine's potential for decreasing the incidence or eliminating neonatal abstinence is of utmost importance. This single factor could provide better acceptance of pharmacotherapy for pregnant opioid-dependent women. Lastly, behavioral and pharmacological interventions can help decrease the number of drug-dependent women in future generations and hopefully improve outcomes for these women and their offspring.

MECHANISMS OF ABUSED DRUGS: CONCORDANCE BETWEEN LABORATORY ANIMAL AND HUMAN STUDIES

K. L. Preston; G. E. Bigelow; L. H. Brauer; W. A. Corrigall; K. A. Cunningham; H. de Wit; L. A. Dykstra; A. J. Goudie; C.-E. Johanson; J. E. Rose; and S. L. Walsh

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The neurochemical mechanisms of action of abused drugs have been studied extensively in laboratory animals and to a lesser extent in humans. The goal of the symposium was to present the findings of human and non-human studies in order to examine the degree of correspondence in the results of the studies across species and the similarities and differences in the methods used to study drug effects in humans and non-humans. The degree of correspondence between human and non-human findings has important implications for the validity and generalizability of studies using animals and may raise important theoretical questions or provide important practical insights regarding the interpretation of results. Data were discussed regarding the neuropharmacological mechanisms of four drug classes: amphetamine; cocaine; opiates; and nicotine.

RECEPTOR MECHANISMS OF AMPHETAMINE STIMULUS PROPERTIES IN NON-HUMANS AND SUBJECTIVE EFFECTS IN HUMANS

L. H. Brauer; A. J. Goudie; and H. de Wit

Results of drug discrimination studies suggest that dopamine mediates the interoceptive effects of amphetamine in laboratory animals. D2 agonists mimic the discriminative stimulus effects of amphetamine in animals and D1 and D2 antagonists block them. The discriminative stimulus effects of drugs in animals are often assumed to parallel their subjective effects in humans, including their euphorigenic effects. However, few studies have directly explored the role of dopamine in the euphorigenic or other subjective effects of amphetamine in humans. Studies that have measured subjective responses to amphetamine after pretreatment with dopamine antagonists have produced mixed results. Studies with subjects who abuse amphetamine have shown that ratings of amphetamine-induced euphoria are decreased by some antagonists, but not others. In contrast, studies with normal volunteers have generally failed to show an effect of dopamine antagonists on euphorigenic or other responses to amphetamine. There are several possible reasons for the discrepant results between animal and human data, and between drug abusers and normal volunteers. Possible methodological reasons include differences in drug use history, amphetamine dose, antagonist dose, and dosing regimen. Possible theoretical reasons include differences in the inferences that are made from different procedures. Future studies with both animals and humans should attempt to evaluate the influence of the methodological differences between studies, and should carefully examine the assumptions made in extrapolations between drug discrimination studies in animals and subjective effects assessments in humans.

SEROTONERGIC MECHANISMS OF COCAINE EFFECTS IN NON-HUMANS AND HUMANS

S. L. Walsh and K. A. Cunningham

Review of the current literature suggests that general enhancement (via precursor administration) or depletion of brain serotonin (5-HT) content (via neurotoxin administration or tryptophan depletion) impacts the reinforcing and subjective effects of cocaine in a manner suggesting that 5-HT plays an overall inhibitory role in these behavioral effects. Selective 5-HT reuptake inhibitors (SSRIs) enhance the discriminability of cocaine and decrease cocaine self-administration in rodents while studies in humans suggest that SSRIs attenuate the subjective effects of cocaine in humans. Unfortunately, attempts to design more definitive analyses of the potential involvement of 5-HT receptor subtypes in the stimulus, reinforcing and subjective effects of cocaine

have been hampered by the paucity of selective agonists and antagonists available for the myriad of 5-HT receptors. Compounds (*e.g.,* Ru 24969) that act as 5-HT1B agonists enhance the discriminative stimulus effects of cocaine in rats although selective 5-HT1A compounds are relatively inactive in this regard. Although few drugs with selectivity for 5-HT2 receptors have been studied systematically, 5-HT2 agonists show some efficacy in attenuating the stimulus effects of cocaine while 5-HT2 antagonists reduce to some extent the reinforcing effects of cocaine in rats. Limited data from humans suggest that 5-HT2 antagonists may decrease the subjective effects of cocaine; thus, 5-HT2 compounds deserve further attention. The majority of studies evaluating the 5-HT3 antagonists have reported negative results across all paradigms. In summary, while the functional significance of 5-HT receptors has not been fully elucidated, these data suggest that changes in serotonergic activity can impact the effects of cocaine in both animals and humans under a variety of experimental conditions. A commonality among the studies with positive findings is that cocaine effects are only partially modified by 5-HT agents regardless of the direction of change.

RECEPTOR MECHANISMS OF AGONIST-ANTAGONIST OPIOIDS IN NON-HUMANS AND HUMANS

L. A. Dykstra; K. L. Preston; and G. E. Bigelow

Data from studies of the discriminative effects of various opioids in laboratory animal and human subjects indicate considerable cross-species generality in the discriminative stimulus effects of opioid agonists. Both laboratory animals and humans can discriminate the presence or absence of opioid agonists, and the resulting discriminations show dose dependency and pharmacological specificity. Laboratory animals can be trained to discriminate among opioid agonists that are selective for mu and kappa opioid receptors. In drug discrimination studies in a number of laboratory animal species, the mixed-action opioids butorphanol and nalbuphine exhibit partial mu agonist activity: they substitute for mu agonists when administered alone and antagonize discrimination of full mu agonists when administered as pretreatments. Butorphanol and nalbuphine rarely substitute for selective kappa agonists; and only modest (very low efficacy) kappa agonist activity has been demonstrated. In contrast, human subjects discriminate butorphanol and nalbuphinc as mu agonist-like under two-choice training conditions (mu agonist vs. saline) but discriminate them as different from mu agonists when a non-mu, non-saline discrimination response is available. The subjective effect profiles of butorphanol and nalbuphine also suggest both mu and non-mu agonist activity. These non-mu effects have been attributed to kappa agonist activity, though no selective kappa agonists or antagonists have been available for human use to confirm this hypothesis. Thus, there is agreement among studies in laboratory animal and human subjects that butorphanol and nalbuphine exhibit partial mu agonist activity and some apparent kappa activity, but less agreement on the extent of their kappa receptor activity. Their relatively lower apparent kappa activity in animal studies may result from comparison to reference drugs with greater intrinsic kappa activity than is the case in human studies. If correct, this interpretation suggests that observed animal-human differences in the classification of opioids with respect to kappa receptor activity may reflect procedural rather than biological differences.

RECEPTOR MECHANISMS UNDERLYING NICOTINE SELF-ADMINISTRATION IN NON-HUMANS AND HUMANS

W. A. Corrigall and J. E. Rose

Studies of nicotine self-administration in animal and human subjects are discussed with respect to the behavioral paradigms employed, the effects of nicotine dose manipulations and nicotinic agonist/antagonist pre-treatment, and the role of neurochemical processes mediating reinforcement. Animal models have focused on intravenous nicotine self-administration, while most studies in human subjects have studied cigarette smoking behavior. Despite procedural differences, data from both animal and human studies show an inverted-U function relating nicotine dose to self-administration behavior, with maximal rates of responding occurring at intermediate doses of nicotine. Moreover, nicotine supplementation via non-contingent nicotine administration suppresses nicotine self-administration behavior in both animal models and human cigarette smokers. Nicotine antagonist treatment also reduces responding, although human studies usually find a transient increase in smoking, which is interpreted as an attempt to compensate for nicotinic receptor blockade. Amongst the neurochemical systems which have been examined, most emphasis has been given to dopamine. The mesolimbic dopamine pathway has been implicated in nicotine reward based on animal studies, and research with humans suggests a role for

dopaminergic processes as well. However, dopaminergic blockade appears to increase cigarette smoking behavior in humans while it attenuates nicotine self-administration in animals. Future research should exploit the complementary aspects of animal models and human paradigms to provide a coherent understanding of nicotine reinforcement. Animal models allow for analysis of anatomical and physiological mechanisms underlying nicotine self-administration; human studies validate the relevance to tobacco dependence and smoking cessation treatment.

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FURTHER CHARACTERIZATION OF A NOVEL CLASS OF NICOTINIC RECEPTOR ANTAGONISTS

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Over the past ten years, there has been a substantial increase in the understanding of brain nicotinic receptors at the molecular level. The structural/functional diversity of these receptors may allow for the development of nicotinic-receptor, subtype-selective agonists and antagonists. The present study investigated the structure-activity relationships (SAR) of pyridine-N substituted nicotines (NIC), constituting a novel class of antagonist. The SAR for analogue-induced inhibition of NIC-evoked [^{3}H]dopamine (DA) release from rat striatal slices and for displacement of t^{3}H]NIC binding from rat striatal membranes was used to probe the interaction with the α3β2 and α4β2 receptors, respectively. S(-)N- Octylnicotinium iodide (NONI) was a potent (IC50=1.3μM) and efficacious antagonist of NIC-evoked DA release. Antagonist potency in the DA release assay was correlated with N-alkyl chain length, up to nine carbons. NIC surmounted the antagonism, suggesting a competitive receptor interaction. In the [^{3}H]NIC binding assay, all analogues tested displaced binding. S(-)N-Decylnicotinium iodide (NDNI) competitively displaced [^{3}H]MC binding and was the most potent (Ki=70 nM) of the analogues. The lack of correlation between inhibition of MC-evoked DA release and displacement of [^{3}HJ]NIC binding suggests that different nicotinic receptor subtypes are involved. Evaluation of analogue-induced inhibition of MC-induced antinociception in the mouse tail-flick assay (probing the α4β2 receptor) revealed that NDNI was a potent (AD50=0.77 μg/mouse, i.t.) and efficacious antagonist, whereas NONI was ineffective. Despite the polar nature of NONI and NDNI, results indicated that they may access the CNS via the choline transporter at the blood-brain barrier. Thus, structural modification of the NIC molecule by pyridine-N substitution converts it from a potent agonist into a potent and efficacious antagonist, and NONI and NDNI may be subtype-selective antagonists.

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A PARAMETRIC STUDY OF INTRAVENOUS NICOTINE SELF-ADMINISTRATION BY HUMANS AND SQUIRREL MONKEYS

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Nicotine was studied as a reinforcer of operant behavior in human volunteers and nonhuman primates (squirrel monkeys). Every 10th press of a lever produced an i.v. injection of nicotine, paired with a light and tone (humans) or a light (monkeys). Each injection was followed by a one min timeout, and daily sessions lasted 3 hr (humans) or 100 min (monkeys). With monkeys, saline and doses of 3, 10 and 30 μg/kg/inj of nicotine were each tested for several sessions. With humans, two levers were available during each session; responding on one lever produced injections of 0.75, 1.5 or 3 mg/inj of nicotine while responses on the second lever produced saline injections. In both humans and monkeys, nicotine injections maintained higher rates of responding than saline injections in most subjects, but overall rates of responding were very low. In order to determine whether higher rates of responding would be maintained at different schedule parameters, the length of the timeout after each injection and the number of responses required to produce each injection were varied. Increases in both response requirement and timeout duration produced marked increases in rates of responding with maximal overall rates of responding during periods when drug was available exceeding one response per second in both humans and monkeys. In contrast, rates of responding maintained by saline injections remained very low. Thus, intravenous injection of nicotine was an effective reinforcer of self-administration behavior in both humans and nonhuman primates when studied under controlled laboratory conditions.

MECAMYLAMINE BLOCKS POSITIVE AND NEGATIVE BEHAVIORAL EFFECTS OF IV NICOTINE IN HUMAN SUBJECTS.

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The ganglionic blocker mecamylamine has been shown to block the positive behavioral effects of IV nicotine, including elevated liking scores and estimates of dose strength. However, blockade of negative effects has not been reported in the literature. The effects of mecamylamine on subjective responses to IV nicotine were evaluated in seven healthy male volunteer cigarette smokers who provided informed consent and resided on the Clinical Pharmacology Research Unit of the ARC. On four separate days, each subject was administered a different dose of mecamylamine (placebo, 5, 10, or 20 mg). One hour later subjects received the first of four doses of IV nicotine (placebo, 0.75, 1.5, and 3.0 mg), followed by injections at one-hour intervals, in a double-blind, placebo-controlled design. Subjective drug responses were collected 15 minutes prior to mecamylamine and at 10 and 45 minutes post-injection. Paired comparisons indicated that mecamylamine significantly decreased scores on the MBG Scale of the ARCI at all nicotine doses. Subjects reported pleasurable effects following 0.75 mg of nicotine and aversive effects following 3.0 mg of nicotine, both of which were significantly blunted by mecamylamine. Mecamylamine also significantly attenuated the dose-related decrease in both tobacco and cigarette craving following 3.0 mg of nicotine. By blocking both the positive and negative effects of IV nicotine, mecamylamine may be useful as an adjunct to nicotine replacement treatment, possibly resulting in fewer side effects and thus, greater treatment success.

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DISCRIMINATIVE STIMULUS, SUBJECTIVE REPORTS AND VIGILANCE EFFECTS OF NICOTINE IN HUMANS

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There are several reports on drug discrimination in humans which have suggested that there is a close relationship between results on the discrimination measures and measures of subjective effect. Discriminative stimulus effects of nicotine were evaluated in humans using conventional behavioural drug discrimination procedures. Moderate smokes (females; n=9) were trained on day 1 to discriminate placebo versus 2 mg nicotine chewing gum. All subjects were able to reach criterion performance (at least 80% correct responses). Generalisation responding across nicotine doses of 0 (placebo), 0.25, 0.5. 1 and 2 mg were then examined on day 2 using a procedure in which subjects reported to what extent the test stimulus resembled the training dose. At the end of each generalisation session subjects performed a vigilance task, which required them to detect a visual stimulus out of a noise background. Subjects were able to distinguish the smallest dose (0.25 mg) from placebo, but the degree to which the test dose resembled the training dose was dose related; same generalisation responding has been obtained with a group of male subjects (n=8). In spontaneous reports subjects to distinguish nicotine reflected change of taste, slight burning of the throat and were dose related but did not correspond to the effects of nicotine on vigilance or in the discrimination procedure. These data indicate a dissociation between subjective reports and the ability to distinguish the nicotine discriminative stimulus in moderate female smokers. Furthermore, these data indicated that the discriminative stimulus effects of nicotine correlates with its vigilance enhancing properties.

CARDIOVASCULAR AND MOOD RESPONSES TO A QUANTIFIED DOSE OF NICOTINE IN ORAL CONTRACEPTIVE USERS AND NONUSERS

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The major aim of this study was to test the hypothesis that women who use oral contraceptives (OCs), compared to nonusers of OCs have larger cardiovascular responses to two standard cigarettes (0.7 mg. FTC nicotine delivery). Acute effects of a standard dose of nicotine on cardiovascular and mood responses in 12 OC users and 12 nonusers were examined after overnight deprivation in two menstrual phases (early follicular and mid-luteal). Each participant attended two experimental sessions in which they first sham-smoked and then smoked two standard cigarettes via a quantified smoke delivery system. OC users exhibited larger nicotine-induced increases in heart rate as compared to nonusers. Acute tolerance to nicotine was found for cardiovascular measures of heart rate, systolic and diastolic blood pressure. A phase-by-time-by- status interaction on systolic blood pressure demonstrated differential acute tolerance to nicotine; during the early follicular phase nonusers of OCs demonstrated less acute tolerance to nicotine during the first 10 minutes following the smoking of the second cigarette. Similarly, hormonal changes associated with the normal menstrual cycle and OC use mediated nicotine-induced mood changes. Nonusers of OCs showed larger reductions in anxiety following smoking as compared with OC users. A phase-by-dose-by-time interaction on anxiety self-reports revealed a significant effect of dose and time during the mid-luteal phase of the menstrual cycle. Taken together, these findings suggest that the female sex hormones mediate nicotine-induced mood and cardiovascular changes. Evidence for cardiovascular hyperreactivity to nicotine in OC users may help to explain the mechanisms by which smoking and OC use combined contribute to an elevated risk for coronary heart disease.

PHARMACODYNAMIC EFFECTS OF COTININE

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The nicotine metabolite cotinine was administered to abstinent cigarette smokers to determine subjective, physiological, and performance effects related to abuse liability and effects on tobacco withdrawal symptoms. Volunteers participated in a five week, double blind, placebo-controlled, inpatient protocol. In four randomly chosen weeks, they were tobacco abstinent for three days and received oral cotinine fumarate (0, 50, 100, or 200 mg) each morning during the abstinence period. The same dose was administered throughout the three day nonsmoking period. In the remaining week, volunteers smoked ad libitum without medication. Results (N=13) indicate tobacco abstinence increased self-ratings of withdrawal, including “depressed mood”, “craving”, and urges to smoke for positive and negative reinforcement (Factors 1 and 2, respectively, on the Questionnaire of Smoking Urges). Cotinine produced no dose-related changes on visual analog scales (VAS) of “drug strength”, “any drug effect”, “good effects”, “bad effects”, “liking”, or “craving”. Cotinine significantly increased ratings of “restless” and “impatience” on the Minnesota Tobacco Withdrawal Symptoms Checklist. Cotinine produced dose related decreases in “depressed mood”. These results lend support to the notion that cotinine is behaviorally active and could mediate certain components of nicotine dependence and/or the tobacco withdrawal syndrome. The lack of effects on VAS suggests cotinine’s effects are subtle and its abuse potential is low.

EFFECTS OF NALTREXONE ON SMOKING AND ABSTINENCE

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Although there is evidence that the opioid system is involved in the rewarding effects of several drugs, it is not clear whether this is the case for nicotine. Studies examining the effects of pharmacological opioid receptor blockade on cigarette smoking have yielded conflicting results. Two studies reported a decrease in cigarette smoking after administration of the opioid antagonist naloxone, while a third failed to find such a decrease. The longer-acting opioid antagonist naltrexone was recently reported not to affect smoking, but to decrease craving during abstinence. Since this could be a clinically important finding; the present study was designed to further examine the effects of naltrexone on smoking and abstinence with emphasis on detecting anti-craving effects during abstinence. Fourteen smokers completed a double-blind, placebo controlled, within-subjects design study. Subjects received naltrexone (50 mg, p.o.) and placebo for four days each, with a 10 day wash-out period between. Order of drug testing was counterbalanced. Subjects reported to the lab daily during each medication phase. During the second visit of each phase, 30 min. *ad lib* smoking was analyzed using smoking topography measures, and physiological and subjective responses to smoking were recorded. Subsequently, subjects were required to abstain from smoking for 72 hours, and withdrawal symptoms and difficulty abstaining were assessed daily. Nahrexone did not affect either smoking behavior or subjective responses to smoking. During abstinence, total score on the withdrawal symptoms questionnaire did not differ between the naltrexone and placebo condition. However, the individual withdrawal symptoms craving, urges to smoke, restlessness and increased eating were all reduced by naltrexone (effects marginally significant, p=0.058-0.075). Difficulty abstaining ratings did not differ between conditions. These findings suggest that naltrexone does not affect smoking behavior, but may influence specific withdrawal symptoms during abstinence including drug craving.

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NORTRIPTYLINE AND COGNITIVE-BEHAVIORAL TREATMENT OF CIGARETTE SMOKING

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Both cognitive-behavioral and antidepressant treatments may be helpful in treating cigarette smokers. Here we present data on the entire sample of 199 subjects at three and six months posttreatment. It was hypothesized that nortriptyline treatment would be differentially efficacious for subjects with a history of major depressive disorder (MDD) in facilitating abstinence, as compared to subjects without an MDD history. Smokers of ten cigarettes per day were randomly assigned to one of four conditions in a 2 X 2 factorial design: cognitive-behavioral mood-management intervention versus standard health education treatment X nortriptyline versus placebo. The present paper reports data from the nortriptyline arm of the study only. Nortriptyline treatment took place during weeks 1-12. Initial nortriptyline dose was 50 mg. for all subjects, and was titrated to blood levels known to be therapeutic for depression. Final dosage was usually between 7.5 and 100 mg./day. Using self-reported abstinence corrected by carbon monoxide and cotinine verification, one-year continuous abstinence rates were 12% for placebo subjects, and 24% for subjects receiving active nortriptyline ($p<.05$). Nortriptyline blood levels predicted continuous abstinence ($p<.02$).

ANALGESIA PRODUCED BY INTRACEREBROVENTRICULAR (ICV) INJECTION OF MORPHINE IN AMPHIBIANS

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Throughout the past decade research exploring the systemic and spinal administration of opioids in amphibians has shown comparable analgesic effect of these compounds in nonmammalian and mammalian vertebrates. With much research attempting to elucidate the complicated patterns of opioid analgesia at spinal and supraspinal sites, a simpler vertebrate model may be useful. It is not known whether non-mammalian vertebrates also contain supraspinal sites mediating opioid analgesia. Thus, mu (morphine, fentanyl), *delta* (DADLE, DPDPE) and *kappa* (U50488, CI977) opioid agents were tested for analgesia using the acetic acid test in the grass frog, *Rana pipiens*. Drugs were given in a volume of 3 µ1 with a microsyringe at a depth of 2.5 mm into the third ventricle. Morphine had an ED50 value of 2.02 (0.9-4.5) nmol/frog. Concurrent naltrexone (1 nmol) significantly blocked the analgesic effect of i.c.v. morphine. Naltrexone administered into the spinal cord prior to i.c.v. morphine produced no effect on analgesia. ED50 values for the six agents ranged from 1.3 to 61.5 nmol/frog with a rank order of potency such that DADLE > morphine > DPDPE > CI977 > fentanyl > U50488. These results show that supraspinal sites mediate opioid analgesia in amphibians and further validate the use of this adjunct or alternative model.

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STUDIES ON THE ANTINOCICEPTIVE ACTIVITY OF DYNORPHIN A-(2-17)

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Dynorphin A-(2-17) possesses antinociceptive and antiedematous properties in rodents (Hooke *et al.* 1995; Thomas and Wei 1995). We have examined the antinociceptive activity of Dyn A-(2-17) against the persistent pain provided by formalin in the mouse paw edema test. A positive result would be of great significance in the enduring search for novel analgesics since this nonopioid peptide has no marked affinity for any of those binding sites traditionally associated with transmission of pain signals (Dr. A. Goldstein, personal communication). Dyn A-(2-17), morphine or saline was given i.v. or i.p. to male mice (25-30 g; n=6-10) 10 min before intrapaw injection of 0.02 ml of 5% formalin and the animals were observed, individually, for paw licking 20 min later (for 10 min). The following A50 values were obtained: Dyn A-(2-17) = 1. 15 (0.59-1.71) and 41.9 (22.5-61.4) umol/kg, i.v. and i.p., respectively; morphine = 0.93 (0.48-1.38) and 2.52 (1.46-3.58) umol/kg, i.v. and i.p., respectively. The peptide-induced antinociception was not evanescent, a dose of 3 umol/kg i.v. giving *Mean % Antinociception* values of 73.3, 41.9 and 24.4 at 0.5, 1 and 2 hr, respectively. The nonopioid nature of this "new generation" analgesic was confirmed since potency against formalin was (a) retained in mice rendered tolerant to the antinociceptive action of morphine and (b) unaffected by naloxone at a dose (10 mg/kg, s.c.) sufficient to block all opioid receptors.

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BIOTRANSFORMATION OF DYNORPHIN A(1-13) AMIDE AND ANTINOCICEPTION IN RHESUS MONKEYS

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Amidation of peptide C-terminals has been suggested as a means to produce compounds with higher stability in biological systems. The present study examined the *in vitro* biotransformation of dynorphin A(1-13)amide [dyn A(1-13)NH2] in rhesus monkey blood incubated at 37°C using matrix-assisted laser desorption/ionization mass spectrometry (MALDI). We also examined its antinociceptive effect in the rhesus monkey warm water tail withdrawal assay (n=3), following intravenous administration. MALDI revealed that intact dyn A(1-13) NH2 survived in blood for up to 5 min, and that amidation protected the C-terminal from enzymatic degradation. However, two other sites of breakdown occurred: one was at the first amino acid position, which yielded dyn A(2-13)NH2, the other was at the 6- amino acid position which yielded dyn A(1-6) and dyn A(7-13)NH2. Neither the parent peptide nor any products were observed after 15 min incubation. Dyn A(1-13)NH2 (3.2 mg/kg, i.v.) was fully antinociceptive in the tail withdrawal assay in 50" water for up to 15-30 min, but was only transiently active in 55° water. This antinociceptive profile was similar to that of the unmodified peptide, dyn A(1-13). Overall, whereas C-terminal amidation protected from carboxypeptidase activity, this did not result in a peptide with a substantially increased or prolonged antinociceptive effect following intravenous administration in rhesus monkeys.

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EFFECTS OF MONOAMINE REUPTAKE INHIBITORS ON THERMAL NOCICEPTION IN RHESUS MONKEYS

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This study characterized the antinociceptive effects of cocaine and selective monoamine reuptake inhibitors administered alone and in combination with morphine in rhesus monkeys. The shaved tails of 4 rhesus monkeys were exposed to warm water (42, 46, 50 and 54°C) and tail withdrawal latencies (20 sec maximum) from each temperature were determined. Cocaine (0.032-1.8 mg/kg) and the selective serotonin reuptake inhibitors clomipramine (0.01-3.2 mg/kg) and fluoxetine (0.1-10 mg/kg) produced small but dose-dependent antinociceptive effects and potentiated the antinociceptive effects of morphine (about a half-log leftward shift). Cocaine (1.8 mg/kg) and clomipramine (1.0 mg/kg) both produced a large potentiation of the antinociceptive effects of the low efficacy μ-opoid agonist nalbuphine, shifting the curve to the left and markedly increasing the maximum effect, but produced no change in the amount of antinociception produced by the high efficacy μ-opioid agonist fentanyl. The selective serotonin antagonist mianserin (0.32 mg/kg) completely suppressed the antinociceptive effects of clomipramine. Mianserin (1.0 mg/kg) produced a half-log unit rightward shift in the cocaine dose-effect curve and attenuated the enhancement of morphine's antinociceptive effects by cocaine (1.8 mg/kg). The selective norepinephrine reuptake inhibitors nisoxetine (0.1-10 mg/kg) and tomoxetine (0.1-10 mg/kg) and the selective dopamine reuptake inhibitiors bupropion (0.032-3.2 mg/kg) and GBR12909 (0.1-10 mg/kg) did not produce antinociception or potentiate morphine-induced antinociception. In fact, GBR12909 produced dose-dependent allodynia, and doses of 3.2 and 10 mg/kg GBR12909 reduced the antinociceptive effects of morphine. These results suggest that serotonergic systems mediate the effects of cocaine on nociception and on morphine-induced antinociception in primates. In addition, these results suggest that serotonergic reuptake inhibitors may be useful as adjuncts to low-efficacy opioids in the treatment of pain,

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CLOCINNAMOX (CCAM) DOSE-DEPENDENTLY ANTAGONIZES MORPHINE-ANALGESIA AND ^{3}H- DAMGO BINDING IN FEMALE RATS

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Clocinnamox is a long-lasting, noncompetitive, *mu*-opioid antagonist in mice and monkeys. The present studies examined the ability of CCAM to antagonize the antinociceptive effects of morphine in rats and to inhibit binding of ^{3}H- DAMGO to rat whole brain homogenates *ex vivo.* Subjects were female Sprague-Dawley rats, 185-290g. Antinociceptive testing used a warm water (50°C) tail-withdrawal procedure; mean baseline tail-withdrawal latencies were 3.8-6.4 sec. Under control conditions, morphine dose-dependently increased tail-withdrawal latencies, the mean baseline ED_{50} of morphine was 5.8Å0.7 mg/kg. Pretreatment with 0.1 mg/kg CCAM did not effect the morphine dose- response curve. A dose of 1.0 mg/kg CCAM displaced the morphine dose-response curve 4-fold to the right of the control curve and 10 mg/kg CCAM eliminated the antinociceptive effects of morphine (10 - 1000 mg/kg) in 50°C water. The antagonism of the antinociceptive effects of morphine by 10 mg/kg CCAM persisted for at least 4 wks. Separate groups of rats received 0. 1, 1.0, or 10 mg/kg CCAM and were sacrificed at various times afterwards. Whole brain membranes were prepared for determination of binding parameters of ^{3}H-DAMGO. CCAM dose-dependently decreased ^{3}H-DAMGO binding *ex vivo* by decreasing B_{max} values, Kd values were not affected by CCAM. Control B_{max} values for ^{3}H-DAMGO binding were 234Å8 fmol/mg protein; in membranes prepared from rats pretreated (24hr) with 0. 1, 1, and 10 mg/kg CCAM, the B_{max} values for ^{3}H-DAMGO were 120Å5, 88Å6, and 54Å2 fmol/mg protein, respectively. The B_{max} values for ^{3}H-DAMGO binding after an injection of 10 mg/kg CCAM returned towards control values gradually. One week after 10 mg/kg CCAM, the B_{max} for ^{3}H-DAMGO was 99Å7 fmol/mg protein, and at two and four weeks after CCAM the B_{max} was 134Å4 and 178Å10 fmol/mg protein, respectively. Our results indicate that CCAM acts as a long- lasting, noncompetitive *mu*-opioid antagonist in rats. Acknowledgments: Supported by NIDA grants DA 00254, DA 07268, and DA 05676.

COLD-PRESSOR PAIN TOLERANCE OF OPIATE ADDICTS ON AND OFF NALTREXONE

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Naltrexone, an antagonist at the p-opiate receptor, is a pharmacotherapy with demonstrated efficacy for the treatment of opiate dependence and, increasingly, the treatment of alcohol dependence. Although naltrexone blocks the analgesic effects of subsequently administered opiates, it is unknown how chronic naltrexone receptor blockade affects the perception of pain in opiate-free individuals with a history of opiate addiction. Consistent with clinical demonstrations of hyperalgesia is acute dosing paradigms of naloxone in normal subjects (Davis *et al.* 1978; Grevert and Goldstein 1977; Levine *et al.* 1979) we hypothesized that naltrexone would decrease pain tolerance by blocking endogenous opiate analgesia during a painful experience. Cold-pressor (CPT) pain tolerance was measured in 10 volunteer, ex-opiate abusing males both during naltrexone maintenance (25 - 50mg/day for at least six weeks) and off naltrexone for an average of 22 days (SD = 29.5 days). Subjects were excluded if suffering from medical conditions affecting pain perception (i.e., peripheral neuropathy), and were drug-free as demonstrated by urine toxicology collected immediately prior to each CPT in the OFF condition. The results reveal a significant decrease (Wilcoxon Matched-Pair Signed-Rank Test, $z = -2.37$, $p = .018$) in CPT pain tolerance OFF naltrexone ($x = 107.8$sec, SD = 113.74) than ON naltrexone ($x = 133.3$sec, SD = 116.79), with change in pain tolerance scores correlated to neither time ON nor time OFF naltrexone. These findings suggest an analgesic effect for naltrexone maintenance, and are worthy of replication in larger samples, including those with a history of alcohol rather than opiate dependence, Possible explanations for naltrexone-induced analgesia, including those unique to opioid-mediated pain systems of opiate addicts (Compton 1994; Vaccarino *et al.* 1988), arc presented. REFERENCES available from senior author upon request.

TREATMENT OF REFLEX SYMPATHETIC DYSTROPHY WITH NALTREXONE

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Reflex Sympathetic Dystrophy (RSD) may occur following trauma, surgery, or several disease states and is one of the most difficult problems for physicians to treat. For patients who do not respond to nerve blocks, reports of pain relief by antidepressants, antiseizure medications, NSAIDs, and opioids have been mixed. Recent animal studies have indicated that narcotic antagonists may be more helpful in attenuating certain types of pain. This analgesia appears to be produced via an increase in kappa receptor activity. Similar findings in humans with thalamic pain syndrome have also been reported. The purpose of the present study was to evaluate the analgesic efficacy of naltrexone in patients with RSD. Five patients with RSD who were not responding to high doses of opioids were gradually withdrawn and started on naltrexone 100-800 mg per day in divided doses. Each patient had an enhanced analgesic effect with naltrexone compared to previous treatment. Two patients had a return of pain after six months. After failure of opioids to provide sustained relief, both patients were placed back on naltrexone with positive results. In all cases, the relief was partial but permitted the patients to become more functional. In four cases, a kappa agonist was added that provided additional analgesia.

NITRIC OXIDE (NO)/CYCLIC GMP SYSTEM AT THE SUPRASPINAL SITE IS INVOLVED IN ACUTE MORPHINE ANTINOCICEPTIVE TOLERANCE

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The role of the supraspinal NO/cyclic GMP system in acute morphine antinociceptive tolerance was investigated using the mouse 55°C warm-water tail-flick test. A single i.c.v. pretreatment of mice with morphine (3 nmol, -140 min) produced an acute antinociceptive tolerance to subsequent i.c.v. morphine, as demonstrated by a 79-fold rightward shift of the morphine dose-response curve. When co-adminstered with morphine (-140 min), N--nitro-L-arginine methyl ester (L-NAME, 0.1-10 nmol), an NO synthase inhibitor, inhibited the development of morphine tolerance in a dose-dependent manner. L-NAME at a dose of 10 nmol, which did not affect morphine-induced antinociception when co-administered with morphine, completely blocked the rightward shift of the morphine dose-response curve caused by i.c.v. morphine pretreatment (3 nmol, -140 min). This effect of L-NAME was partially antagonized by L-arginine, but not D-arginine in a dose-dependent manner. Methylene blue (MB, 1-10 nmol), a guanylate cyclase inhibitor, when co-adminstered with morphine (-140 min), were also able to block the acute morphine antinociceptive tolerance, thought it exhibited lower efficacy compared with L-NAME because only partial reversal of the acute morphine tolerance was observed with 10 nmol of MB. The effects of increased production of NO on acute morphine antinociceptive tolerance were also studied. When co-adminstered with morphine (-140 min), neither L arginine (100 nmol) nor the NO donors, sodium nitroprusside (5 nmol) or isosorbide dinitrate (10 nmol) affected the 6-fold rightward shift of the morphine dose-response curve caused by i.c.v. morphine pretreatment at a lower dose (1 nmol, - 140 min). L-Arginine when given i.p. at dose of 200 mg/kg daily for three days, did not produced any change in the magnitude of the acute morphine antinociceptive tolerance. Together, our results indicate that the supraspinal NO/cyclic GMP system is involved in the development of acute morphine antinociceptive tolerance. However, increased production of NO does not affect the magnitude of morphine tolerance. ACKNOWLEDGEMENTS: Supported by USPHS grants DA03742 and DA07232.

ANALGESIC TOLERANCE IN NEONATAL RATS CONTINUOUSLY RECEIVING FENTANYL BY OSMOTIC MINIPUMP

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Our survey data and a review of the literature indicate that the attitudes and practices of clinicians in the areas of neonatal pain management have changed. Today neonates arc more readily treated with opioids than in the past. However, the judicious use of opioids are hampered by reports of analgesic tolerance and physical dependence in neonates continuously receiving morphine or fentanyl during painful and stressful life-saving procedures. Little is known about the vulnerability of neonates to become tolerant. Animal models to investigate tolerance have been reported, yet nothing is known about the vulnerability of neonates to become tolerant. Animal models of neonatal tolerance have been reported, yet nothing is known about fentanyl. We hypothesized that continuous fentanyl administration would render neonatal rats tolerant to fentanyl. Initial experiments were conducted to evaluate the acute antinociceptive effects of s.c. fentanyl in postnatal day 9 (P9) rats using the tail-flick test. The ED50 value was 19 µg/kg (95% C.L. 10 to 39). Other neonatal rats at P6 remained naive, or were surgically implanted with Alzet 1003D osmotic minpumps containing saline and fentanyl. Fentanyl infused for 72 hrs at 100 µg/kg/hr was calculated to maintain an initial 84% antinociceptive effect. In fentanyl-infused & neonates at P9, the potency of fentanyl was decreased 4.8-fold compared to saline-infused neonates. The ED50 values were: Naive, 19 µg/kg (95% C.L. 12 to 29); Saline-infused, 31 µg/kg (95% C.L. 18 to 52); Fentanyl-infused, 83 µg/kg (95% C.L. 59 to 116). In fentanyl-infused female rats the potency of fentanyl was decreased 5.2-fold compared to saline-infused neonates. The ED50 values were: Naive, 23 µg/kg (95% C.L. 16 to 33); Saline-infused, 17 µg/kg (95% CL. 10 to 28); Fentanyl-infused, 91 µg/kg (95% C.L. 45 to 184). Thus, continuous fentanyl administration rendered both male and female rats equally tolerant to fentanyl. This work was supported by NIDA grant P50-DA-05274.

ETONITAZENE ANALGESIA IN RATS: ANTAGONISM, TOLERANCE AND CROSS-TOLERANCE STUDIES.

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The analgesic effects of etonitazene, a high efficacy µ opiate, were characterized in the rat tail-withdrawal assay. Latency to tail-withdrawal from 40° and 55°C water was measured and a 15-s cut-off latency was imposed. Etonitazene (0.00032.0.01 mg/kg) produced dose-dependent increases in % maximum possible effect. Naltrexone (0.01-1.0 mg/kg) and nalbuphine (3.2-32 mg/kg) produced dose-dependent antagonism of the analgesic effects of etonitazene with µ opioid apparent pA_2 values. Clocinnamox (10 mg/kg, s.c.) significantly decreased the etonitazene ED_{50} by lo-fold, without decreasing maximum effect. Repeated treatment with escalating doses of etonitazene (0.001-0.128 mg/kg per day) produced greater cross-tolerance to lower efficacy agonists such as buprenorphine than to the higher efficacy agonists such as etonitazene. To equivalently alter the etonitazene ED_{50} by 10-fold, the following repeated treatment doses were required: 0.8 mg/kg per day buprenorpohine (< 20 x the buprenorphine ED_{50}); 160 mg/kg per day morphine (50 x the morphine RD_{50}); and 0.128 mg/kg per day etonitazene (70 s the etonitazene ED,,).

These data confirm that etonitazene produces analgesic effects through a high efficacy µ opioid mechanism in rats. Furthermore, these data support the hypothesis that magnitude of tolerance to the analgesic effects of µ opioids is inversely related to the relative efficacy of the agonist tested as well as the agonist used as the repeated treatment agent.

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REINFORCEMENT OF COCAINE ABSTINENCE IN TREATMENT-RESISTANT PATIENTS: EFFECTS OF REINFORCER MAGNITUDE

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Voucher-based reinforcement of cocaine abstinence has successfully produced sustained cocaine abstinence in some methadone patients, but failed in others. This ongoing study assesses whether we can promote sustained cocaine abstinence in the subgroup of treatment-resistant patients by increasing the magnitude of voucher reinforcement. Participants are 29 methadone patients who previously failed to achieve sustained abstinence when exposed to a 13-week intervention in which they could earn up to $1155 in vouchers (exchangeable for goods/services) for providing cocaine-free urines. Each patient is being exposed, in counterbalanced order, to three 9-week voucher interventions (separated by 4-week baseline periods), in which they can earn up to $0, $380, or $3,400 in vouchers. Sixteen patients completed all three voucher conditions. Analyses of urine samples from those 16 patients showed that the longest duration of sustained cocaine abstinence was related to voucher magnitude ($F=13.42$; $df=2,30$; $P<.001$); means were .27, .81, and 3.79 weeks, during zero, low and high pay conditions, respectively. Half of the patients in the high magnitude condition achieved four or more weeks of sustained cocaine abstinence, whereas only one patient in the low magnitude condition and no patients in the zero magnitude condition achieved more than two weeks of sustained abstinence. These results show that high magnitude voucher-based abstinence reinforcement can promote sustained cocaine abstinence even in treatment-resistant patients. This study represents an initial step in developing an effective treatment for this difficult population of cocaine-abusing methadone patients.

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MONETARY REINFORCEMENT OF COCAINE ABSTINENCE IN COCAINE-DEPENDENT SCHIZOPHRENIC PATIENTS

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Contingency management has been used to modify behaviors in both schizophrenia and substance abuse. This study was designed to determine whether contingency management could reduce cocaine use by schizophrenics. Two male outpatients met DSM-III-R criteria for schizophrenia and cocaine dependence. They were homeless, actively psychotic and frequent cocaine users despite enrollment in a comprehensive dual diagnosis treatment program. This study used an A-B-A design with each phase lasting two months. During the intervention phase, subjects provided a daily urine specimen which was tested for cocaine using a rapid qualitative test. If this test was negative, they were paid $25 in cash. To determine the efficacy of this intervention, the study used an additional and quantitative urine toxicology method. Twice weekly, in all three phases, subjects provided a urine specimen which was assayed for the cocaine metabolite, benzoylecgonine, using fluorescence polarization immunoassay and high-pressure liquid chromatography. The mean concentration of benzoylecgonine was significantly lower during the invention (4.9K ng/ml; 1.9K-13K = 95% confidence limit) than during the baseline (19K ng/ml; 7.3K-49K = 95% confidence limit, $t(49)=2.75$, $p=.009$). During the post-intervention phase, the concentration was intermediate, but not significantly different from either baseline or intervention levels. These results suggest that modest monetary reinforcement of abstinence may decrease cocaine use among cocaine dependent schizophrenic patients. Therefore, it may be possible to reduce cocaine use by distributing a portion of monthly disability income to patients contingent on abstinence..

A CONTROLLED COMPARISON OF TWO VOUCHER SYSTEMS FOR COCAINE ABSTINENCE

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We compared treatment outcomes of 23 minority, inner-city, crack cocaine-dependent patients receiving different voucher systems for cocaine abstinence. All patients received individual cognitive-behavioral counseling as well as group sessions on interpersonal problem-solving and relapse prevention. All were required to submit three urine samples weekly. Samples were temperature tested to ensure veracity and analyzed on site by Emit® for presence of the cocaine metabolite benzoylecgonine. Patients were informed of the urinalysis result by presentation of a feedback slip. The slips sometimes had a dollar value attached to them, making them vouchers that patients exchanged for goods and services consistent with encouraging drug-free activities and lifestyles. Twelve of the subjects were randomly assigned to receive vouchers according to Voucher Schedule 1 and eleven were assigned to Schedule 2. Both schedules provided differential reinforcement of cocaine abstinence, but they differed along six dimensions. The group receiving vouchers according to Schedule 2 had greater number of cocaine-free urines ($F(1,21) = 5.7$, $p=.03$), greater number of completely drug-free urines ($F(1,21) = 5.6$, $p=.03$), and longer durations of continuous cocaine abstinence ($F(1,21) = 6.5$, $p=.02$). Schedule 2 provided: (i) more immediate consequences, (ii) greater reinforcer magnitude for initiating abstinence, (iii) higher possible voucher earnings, and (iv) increasing reinforcer intermittence with increasing abstinence, and did not provide: (v) a response-cost for cocaine positive urines or (vi) differential reinforcement for sustained cocaine abstinence. These data suggest some important dimensions of reinforcement scheduling to consider in designing and evaluating voucher incentive systems in cocaine treatment.

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EFFICACY OF INCENTIVES DURING OUTPATIENT BEHAVIORAL TREATMENT FOR COCAINE DEPENDENCE

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Our group has been researching the efficacy of a voucher-based incentive program in outpatient treatment for cocaine dependence. Vouchers exchangeable for retail items are earned contingent on cocaine-negative urinalysis results. In two prior trials, patients who received this incentive program in combination with counseling based on the Community Reinforcement Approach (CRA) were retained in treatment longer and achieved greater periods of cocaine abstinence than patients assigned to drug abuse counseling. A third trial isolated the efficacy of vouchers by comparing outcomes in patients who received CRA with versus without vouchers. Those who received vouchers were retained in treatment longer and achieved greater periods of cocaine abstinence than those in the group without vouchers. In each of those trials between-group differences in retention rates obscured determination of whether vouchers directly reinforced cocaine abstinence. To address that issue, a 24-week trial is being conducted comparing CRA with vouchers contingent on cocaine abstinence versus CRA with vouchers earned noncontingently. *Preliminary* results are available based on 61 subjects. As planned, retention rates were comparable across the two groups. Nevertheless, significantly more patients assigned to the contingent than the noncontingent voucher group achieved $\geq$ nine weeks of continuous cocaine abstinence (44%) vs. 21%, $p \geq 0.05$). These results provide further support that contingent vouchers can directly reinforce periods of sustained cocaine abstinence in dependent outpatients.

CONTINGENCY MANAGEMENT INTERVENTIONS IN THE TREATMENT OF COCAINE-DEPENDENT PATIENTS INFECTED WITH TUBERCULOSIS

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Drug abusing patients who have been exposed to tuberculosis are a high risk for developing active TB disease. Poor compliance with prophylactic treatment leads to increased likelihood of developing active disease, and continued cocaine use leads to a greater engagement in high-risk behaviors. The **purpose** of this ongoing study is to determine the relative effectiveness of contingency management interventions, as adjuncts to baseline treatment, in decreasing cocaine use and increasing compliance with chemoprophylactic treatment. **Methods:** Patients with a primary diagnosis of cocaine dependence, or opiate dependence with secondary cocaine dependence, are randomly assigned to one of three treatment groups. Patients in all three groups receive baseline treatment: behaviorally based counseling, isoniazid, TB education and routine liver function tests. Patients are required to attend clinic (3/week) and provide a urine sample at each visit. In addition to the baseline treatment, patients in Group A are reinforced ($18) for each cocaine-free UA, with an additional weekly reinforcer ($20) if they attend clinic all three days and all three UAs per week are cocaine-free. Patients in **Group B** are reinforced for each decrease in cocaine metabolite levels, ($15). Patients also receive a larger reinforcer ($18) for each cocaine-free UA, and an additional weekly reinforcer ($20) if they attend clinic on all three days and three of the Uas per week demonstrate a decrease in cocaine use or are cocaine-free. Patients in **Group C** receive baseline treatment alone (Control group). **Results:** Data are presented on 26 patients. Both contingency groups (CMI) are combined and compared with the control groups. (a) Treatment retention: Significantly more patients in the CMI groups (80%) remained in treatment, compared to the control group (34%) [p=0.017]. (b) Cocaine abstinence: Patients in the CMI groups had higher rates of cocaine-free UAs (71%), than in the control group (45%)[p=0.081]. (c) INH Compliance was very high in all groups (90% of medication was taken), but was significantly higher in the CMI groups (95%) than in the control group (83%)[p=0.016]. **Conclusions:** CMIs enhance treatment retention, cessation of cocaine use and compliance with INH. These data have important health care benefits. **Acknowledgements:** Supported by NIDA grant DA 08644

ADDING SOCIAL NETWORK EXERCISES TO ANTI-CRAVING TOOLS IN COCAINE TREATMENT

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Our research group has previously demonstrated that patients taught a series of **active tools** for countering cue induced **craving** had improved drug use outcomes compared to randomly-assigned control patients who received equivalent amounts of professional attention. As problems in the patients' social network may also constitute a risk for relapse, we have recently developed a complementary treatment component to address this risk. The component consists of a series of manual-guided **social network exercises** which encourage positive interpersonal relationships and help minimize the impact of negative social interactions. The exercises are taught in individual sessions, and include *Communication; Trust; Enjoyment/Satisfaction; Daily Hassles; Handling Problems and Conflicts; and Intimacy.* We are now evaluating the treatment outcome of cocaine patients (n=35 entered into the study; n-22 included in the data set) randomized either to a combination of anti-craving tools and social network exercises or to an equivalent amount of professional attention in an ongoing 12 week protocol. Both the experimental and control conditions are added to a standard treatment baseline of weekly drug counseling and regular urine monitoring. Interim analyses of drug use and retention data will be presented for the ongoing study.

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THE EMPLOYMENT OF A COCAINE TRIGGER INVENTORY IN RELAPSE PREVENTION TREATMENT PROGRAM

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As a part of a relapse prevention psychotherapy program with cocaine abusers, high risk situations were identified at the time of the two initial therapy sessions by employing G. D. Shulman's Cocaine Trigger Inventory (1989) which lists situations and cues that could trigger craving for cocaine. In the course of developing a manualized 12-week program of Cognitive-Behavioral-Interpersonal Integrated Counseling it became evident that the inventory was used in exploring the mechanism of cocaine use cessation and relapse. In this study, Inventory responses from 90 ambulatory research treatment volunteers were examined to evaluate the utility of the instrument. Subjects were mostly African-American males, and 40% were successful at completing the required eight or 12 weeks of counseling. Among these subjects, craving was most frequently triggered in cocaine focused situations that involved use by subjects' friends and co-workers. A classification function derived from a logistic regression and factor analysts of situations and cues predicted overall retention rates with 70% accuracy. Work-related situations were most instrumental in differentiating dropouts from completers. Overall, findings were consistent with Shulman's original validation study of 200 addicts at two residential treatment facilities. However, research is needed to match treatment techniques to specific situations and cues identified by the questionnaire further assess the clinical utility of the Inventory.

ABSTINENCE CONTINGENT HOUSING ENHANCES DAY TREATMENT FOR HOMELESS COCAINE ABUSERS

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Day treatment/work therapy with abstinent contingent housing (DTWH) was compared to the same treatment without housing or work therapy (DT) for homeless, dually diagnosed, cocaine abusers on outcomes of addiction and homeless severity at baseline, weekly, and after two months treatment. DTWH was hypothesized to show better outcomes. Consenting subjects (n=72) were randomly assigned and assessed by independent interviewers. Days homeless, homelessness severity, and urine toxicologies were examined. DT involved unique goals established during assessment, random urines 2/wk, individual and multiple group counseling 6 hr/day for two months in a milieu using vouchers to reinforce non-drug related social/recreation activities. Transportation to/from shelters and lunch were provided. DTWH subjects developed employment goals and could work refurbishing managed housing, available for a modest rent, contingent on abstinence. Weekly toxicology results for DT(n=16) respectively, show consecutive weeks drug free = 5.1 SD=2.7 vs 3.3 SD-2.7 (Mann Whitney U p <0.02) with frequency of consecutive weeks drug free for DTWH skewed toward six and eight weeks while frequency for DT was skewed toward <6. Homelessness outcomes did not differ at baseline, but distributions for DTWH showed lower levels than DT for both days homeless (median 21 vs 58) and homelessness severity (median of 9.4 vs. 12.4) with significant difference in the distributions demonstrated by the Kolmogorov-Smirnov test (p=0.03 for days and p-0.01 for severity). Results suggest a strong therapeutic effect for abstinence contingent housing and work therapy as adjunct to day treatment and that such contingencies alone may be sufficient intervention for homeless substance abusers without serious mental disorders.

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QUANTITATION OF mRNAs FOR KAPPA AND MU OPIOID RECEPTOR AND DYNORPHIN AND ENKEPHALIN IN HUMAN BRAIN BY RNase PROTECTION AND SCINTILLATION ANALYSIS

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Pilot studies were performed to determine the feasibility of quantitating opioid mRNAs in human brain. Selected brain regions were obtained from three post-mortem brain specimens. The mRNA was extracted and assayed for opioid mRNA density by TCA precipitation of RNase protected mRNA-cRNA hybrids using riboprobes generated from the recently cloned human kappa (hKOR) and mu (hMOR) opioid receptors as well as the human dynorphin (hDYN) and enkephalin (hENK) cDNAs. Data are expressed as attomoles specific mRNA/µg total RNA. Only one region, the lateral frontal pole (LFP), was available from the first subject, an 81 year old male who had laryngeal cancer. Additional brain regions including, medial frontal pole (MFP), caudate (CAU), putamen (PUT), and substantia nigra (SN) were obtained from the second subject, a 69 year old female with heart disease. From the third subject, a 76 year old female with pancreatic cancer, additional regions including nucleus accumbens (NAC), globus pallidus (GP), thalamus (THA), and cerebellum (CER) were obtained. With this assay we are able to quantitate and compare opioid mRNA densities in human brain.

EXPRESSION OF µ AND κ OPIOID RECEPTORS BY NORMAL AND DYSMYELINATING OLIGODENDROCYTES DURING *IN VITRO* DEVELOPMENT

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Opioids have previously been shown to inhibit astroglial proliferation during CNS development. The effects of opioids on the other CNS macroglial cell, the oligodendrocyte (OL), have not been rigorously investigated. To determine whether OLs might respond to opioids during maturation, we assessed the expression of µ, κ and δ opioid receptors on developing Ols *in vitro.* Primary glial cultures from mouse cortex were established using standard mechanical and enxymatic dissociation techniques. Immature O1s were dislodged from the surface layer of 7-8 day primary cultures and further purified by panning to remove more strongly adherent astroglia. Enriched OL cultures were immunostained at 1-7 days after plating using polyclonal antibodies directed against κ, µ and δ opioid receptor types (Dr. R. P. Elde, Univ. Minnesota). To positively identify O1s, some cultures were double-stained with either the monoclonal O4 antibody or a monoclonal antibody to myelin basic protein (MBP). O4 detects sulfatide, an early glycolipid marker of OL differentiation. All O4 immunoreactiveO1s co-expressed µ type opioid receptors. Expression of µ receptors was confined to discrete, perinuclear regions regardless of the culture age. O1s also expresseded κ type opioid receptors, but only at later stages of differentiation when they also expressed markers such as MBP. Reaction product for κ receptors was more widely distributed in OL cell bodies and extended into some cell processes. O1s did not express δ receptors at any time. We also examined O1s enriched from cortices of Jimpy mice. Jimpy is an X-linked mutation which results in a failure of OL differentiation, premature OL death and severe CNS hypomyelination. Although µ receptors appear to be expressed normally in jimpy O1s κ receptors are not present even in the few mature jimpy O1s which express MBP. Collectively these findings suggest a sequential expression of µ and then κ opioid receptors during normal OL development. That κ receptor expression is abnormal in O1s from a dysmyelinating mutant underscores the likelihood that opiates play important roles in normal OL maturation. Supported by NMSS RG2461A1 and NIH DA06204

CHARACTERIZATION OF AMPHETAMINE, CATHINONE, NEXUS, DOB, MBDB, HMDMA, MDM-1-EA AND N-OH-MDMA IN FEMALE RATS TRAINED TO DISCRIMINATE MDMA

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Female Long-Evans hooded rats were trained to discriminate 1.5 mg/kg (±)-3,4-methylenedioxymethamphetamine (MDMA) from water in a 2-lever drug discrimination procedure. Amphetamine and several structurally related "designer drugs" were then tested for substitution. These included (±)-cathinone (0.32-3.2 mg/kg), (±)-N-methyl-3,4-methylenedioxyphenyl-2-butanamine (MBDB or "Fido Dido", 0.1-3.2 mg/kg), (±)-N-OH-3,4-methylcnedioxymethamphetamine (N-OH-MDMA or "Flea", 0.1-3.2 mg/kg), 4-bromo-2,5-dimethoxyphenethylamine ("Nexus", 0.1-1.5 mg/kg), 4-bromo-2,5amphetamine (DOB, 0.32-3.2 mg/kg), N-metliyl-1-(3A-methylenedioxyphenyl)-1-ethanamine (MDM-1-EA) and N-methyl-1-(3,4-methylenedioxyphenyl)-3-butanamine (HMDMA). In a previous study in male rats (Bronson *et al.,* 1994) HMDMA substituted for MDMA in 5/7 rats and MDM-1-EA produced partial substitution. In female rats, however, no dose of either drug substituted for MDMA. Cathinone and amphetamine partially substituted for MDMA in female rats, which is similar to findings in male rats (Schechter 1989). Nichols and Oberlender (1989) reported that both (+)- and (-)-MBDB substituted for MDMA in male rats, and in the present study racemic MBDB also substituted for MDMA in female rats. Similarly, Glennon and Misenheimer (1989) reported that N-OH-MDMA substituted for MDMA in male rats, and this compound also substituted for MDMA in female rats. DOB and Nexus, two brominated amphetamine derivatives, also substituted completely for MDMA but DOB did so only at doses that significantly decreased responding. In addition, Nexus proved to be very disruptive after testing, in that animals continued to respond on the MDMA lever for several days after administration of Nexus, suggesting that this drug produces long-lasting effects.

References may be obtained from the fist author.

INTERACTION BETWEEN MORPHINE AND SOCIAL STRESS ON FOS EXPRESSION IN MOUSE BRAIN STEM

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Stressful social confrontations have long-term consequences for opioid analgesia and tolerance (Miczek *et al.,* 1991). In order to clarify potential molecular mechanisms of this phenomenon we studied expression of immediate early gene c-fos, which serves as marker of neuronal activity. Fos immunohistochemistry was used as a method for detection c-Fos protein in mouse brain stem structures after "social stress", to which the mice were subjected immediately for one week before administration of morphine. Mice were perfused one hour after i.p. morphine. Acute injection of morphine (7.5 mg/kg and 10 mg/kg) induced Fos expression in locus coeruleus (LC) and in periaqueductal gray (PAG) that was substantially higher than in control mice. Social stress immediately before morphine injection (7.5 mg/kg) had an addictive effect on Fos immunoreactivity in PAG and LC, the number of Fos-positive nuclei tended to be higher than after morphine alone. On the other hand, social stress, given to mice one week before morphine injection, attenuated c-fos expression in PAG, and this expression was similar to that after saline. Estimation of mu receptors in *in situ* hybridization did not reveal significant differences in number of mu receptors between mice with morphine alone or in combination with social stress. These results suggest an important role of c-fos expression in PAG in the process of tolerance after social stress and morphine.

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PHARMACOLOGICAL MECHANISMS IN THE DISCRIMINATIVE STIMULUS EFFECTS OF BENZTROPINE ANALOGS

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Benztropine inhibits the reuptake of dopamine with potency equivalent to that of cocaine, but it does not share the behavioral profile of classic psychomotor stimulants. Based upon these behavioral differences, it has been suggested that benztropine may have therapeutic utility as a replacement therapy for treatment of cocaine dependence. The subjective effects of benztropine have been explored in a preclinical model using drug discrimination procedures. Previous work has suggested that substitution for the discriminative stimulus effects of benztropine is determined primarily by antagonist effects at M_1 cholinergic receptors. In the present study, Sprague-Dawley rats (n=12) were trained to discriminate 3 mg/kg benztropine from vehicle using standard operant techniques. Evaluation of a series of 3', 4'- and 4',4"-substituted benztropine analogs with varying affinities for both MI receptors and the dopamine transporter yielded varying degrees of partial substitution. Over 75% substitution was achieved with 3'-Cl, 2'-F, 4'-Cl, and 4',4"-diF benztropine analogs, despite a range of affinities for the dopamine transporter, whereas ED_{50}s for these compounds were correlated with M_1 affinity. Benztropine analogs with relatively lower affinity for M_1 sites, 4',4"-diC1 and N-nor-4',4"-diF analogs, did not substitute for the discriminative stimulus effects of benztropine. However, the b-4'-Cl and 2'-NH2 analogs did not substitute for the discriminative stimulus effects of benztropine despite their high affinity for M_1 sites, although they did produce decreases in rates of responding. Although blockade of M_1 cholinergic receptors appears to be the primary determinant of benztropine substitution, further pharmacological evaluation is underway to clarify mechanisms involved in the subjective effects of these compounds.

LEWIS AND FISCHER RAT STRAIN DIFFERENCES IN ACQUISITION BUT NOT MAINTENANCE OF COCAINE BEHAVIORS

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Lewis (Lew) and Fischer 344 (F344) inbred rat strains differ in behavioral and biochemical responses to drugs of abuse and may provide a model to study genetic factors involved in vulnerability to drug abuse. To test this, we compared Lew and F344 rats in acquisition of cocaine (COC) self-administration. Rats (n's=10-20), implanted with chronically-indwelling jugular catheters, were allowed 15 days to acquire this operant at one of three training doses (0.25, 0.5, or 1.0 mg/kg/infusion) in daily, 2 hr sessions (FR1). Acquisition was defined as when active lever bar press rates exceeded the 99% confidence interval of inactive bar press rates for three consecutive days. Rats that acquired were tested for dose-related responding. Compared to F344, Lew rats acquired COC self-administration at lower doses and after fewer training trials. Yet, there were no strain differences in dose-related responding after acquisition. Other Lew and F344 rats (n_s=5-8) were trained to discriminate COC (10 mg/kg, i.p.) from vehicle in a two-lever, food-reinforced (FR10) procedure. Once COC demonstrated control over behavior (6 consecutive days of $\geq$ 90% drug-appropriate responding), generalization tests with COC (0.3-10 mg/kg) were run. No strain differences in acquisition of COC discrimination were seen; the number of trials to reach criterion were 42.7 ± 6.8 for Lew and 35.9 ± 3.4 for F344 rats. Dose-related responding to COC was demonstrated, with no strain differences: ED_{50s} were 1.2 mg/kg (Lew) and 1.8 mg/kg (F344). Compared to F344 rats, Lew rats had higher response rates across doses. Finally, COC plasma levels were assessed in Lew and F344 rats (n_s=5) from 5-30 min after i.v. COC (1 mg/kg; 10 sec) infusions and no strain differences were seen. Strain differences in acquisition but not maintenance of COC behaviors are likely not due to pharmacokinetic differences and may be related to differences in the mesolimbic dopamine system. These results provide support for me use of these strains to study factors underlying vulnerability to COC abuse.

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STRESS, CORTICOSTERONE AND THE DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE

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The ability of the interoceptive cues produced during stress to substitute for the discriminative stimulus properties of cocaine was investigated. Adult male Wistar rats were trained to discriminate cocaine (10 mg/kg i.p., n=10; or 20 mg/kg i.p., n=6) from saline using a two-choice, operant, food-reinforced, drug discrimination task. Restraint stress (15 min.) administered immediately following an injection of saline (i.p.) partially substituted for cocaine (10 and 20 mgkg) without affecting discrimination when delivered following injections of either dose of cocaine. Intermittent electric footshock (15 min. session, 0.6 mA, 0.5 msec duration, every 30 sec.) and conditioned fear (10 sec. tone and stimulus light paired with the delivery of electric footshock under a random-interval 5 min. schedule during daily 60 min. sessions for 2 weeks) each also partially substituted for both doses of cocaine when administered following injections of saline. Similarities between the discriminative stimulus properties of stress and cocaine supports the hypothesis that these interoceptive cues are produced by the activation of common effector systems. Since corticosterone secretion is enhanced during stress as well as following cocaine administration, the role of corticosterone in the discriminative stimulus properties of cocaine was investigated using the adrenocorticosteroid synthesis inhibitor/ Type II receptor antagonist, ketoconozole. Pretreatment with ketoconozole (25, 50, or 100 mg/kg i.p) failed to attenuate the discriminative stimulus properties of cocaine in rats trained to discriminate cocaine (10 mg/kg) from saline.

ACKNOWLEDGEMENTS
Supported by USPHS grant DA06013 from the National Institute on Drug Abuse

CHARACTERIZATION OF THE ROLE OF 5-HT, NE, AND DA IN THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE

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Dopaminergic mechanisms are thought to be responsible for many of the behavioral effects of cocaine, but there is also evidence that other monoamines may be involved in, for example, its discriminative stimulus (DS) and reinforcing effects. In order to further analyze the role of 5-HT and NE in the DS effects of cocaine, rats (N=18) were trained to discriminate a low dose (2.5 mg/kg, i.p.) from a high dose of cocaine (10 mg/kg) in a two-lever, FR10 drug discrimination paradigm, and the ability of monoamine reuptake blockers to enhance the effects of the low training dose was examined by administering compounds (t-30 min, i.p.) in combination with the low dose (t-15 min). The 5-HT reuptake blockers fluoxetine (ED_{50}: 3.4 mg/kg), paroxetine (1.3), and alaproclate (4.4), the NE reuptake blockers desipramine (0.58), nisoxetine (7.1), and nortriptyline (4.6), the mixed compounds bupropion (6.4), cocaine (1.7), imipramine (5.3), mazindol (0.38), and nomifensine (1.3), and the DA reuptake blocker GBR 12935 (5.7) all produced high-dose lever (HL) selection in a dose-related manner, with maximal effects of 80-100% HL selection. Because NE and 5-HT reuptake blockers engendered HL selection only when administered in combination with cocaine, these results indicate that the DS effects of the high dose of cocaine are mimicked by the addition of a low dose and 5-HT and/or NE reuptake blockade. Although these findings may be explained by 5-HT/DA or NE/DA interactions, they are also consistent with the idea that 5-HT and NE are important components of the DS effects of cocaine in the rat.

SUBTLE DIFFERENCES IN THE DISCRIMINATIVE STIMULUS PROPERTIES OF IV COCAINE VERSUS GBR 12909 IN RATS

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The ability of cocaine to bind to dopamine transporters is considered the primary mechanism by which it produces its strong reinforcing and behavioral effects. Recently, we have reported that IV cocaine, besides producing dopamine-dependent effects, also produces initial brief and intense behavioral and cardiovascular effects, that appear to be independent of dopamine, serotonin, or norepinephrine transporters or sodium channel mechanisms. Dopamine-selective reuptake inhibitor, GBR 12909, norepinephrine-selective reuptake inhibitors, desipramine and nisoxetine, serotonin-selective reuptake inhibitor, fluoxetine, and sodium channel blockers, lidocaine, lack these initial effects (Tella, 1996). In the present study using an IV drug discrimination procedure, we further evaluated the differences between cocaine and GBR 12909. Male Sprague-Dawley rats in group 1 were trained to discriminate cocaine (1 mg/kg) from saline (1 ml/kg), while rats in group 2 were trained to discriminate cocaine (1 mg/kg) from GBR 12909 (1 mg/kg) or saline (1 ml/kg), using a fixed ratio 10 schedule of food reinforcement. Rats in both groups learned the required discriminations. However, rats in group 2 needed approximately twice the sessions as rats in group 1. Cocaine (0.3-3 mg/kg) dose-dependently substituted for cocaine in both groups. In contrast, GBR 12909 (0.56-1.56 mg/kg) and its analog, GBR 12935 (0.3-1.56 mg/kg), dose-dependently substituted for cocaine in group 1, but not in group 2. The norepinephrine-selective reuptake inhibitors, nisoxetine and desipramine, the serotonin-selective reuptake inhibitor, zimeldine or sodium channel blocker, lidocaine, produced little or no substitution for cocaine in either group. These data indicate that there are differences in the discriminative stimulus effects of IV cocaine versus GBR 12909. These differences appear to be independent of the effects of cocaine on dopamine, norepinephrine or serotonin transporters or sodium channels.

REFERENCES: Furnished on request of senior author. Supported by NIDA #DA08830 and NIDA IRP.

COMPARISONS OF REINFORCING AND DISCRIMINATIVE STIMULUS EFFECTS OF I.V. COCAINE IN RHESUS MONKEYS

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The reinforcing and discriminative effects of cocaine were compared in different groups of four rhesus monkeys each. Reinforcing effects were studied on responding maintained under a multiple fixed-ratio (FR) 30 food, FR 30 cocaine-delivery, TO 10 min schedule. Responding was well-maintained when the unit dose and number of drug deliveries per component were reduced to 10 μg/kg/inj and one delivery per component. However, lower unit doses failed to consistently maintain responding. Discriminative stimulus effects of cocaine were studied by first training the monkeys to discriminate i.v. injections of cocaine (100 μg/kg) from saline, using FR 40 schedules of food presentation, and then fading the training dose to lower doses of cocaine. Under these conditions discriminative control could not be maintained with doses lower than 17 μg/kg. These results suggest that cocaine exhibits reinforcing effects at doses slightly lower than those capable of sustaining drug discrimination, and imply that the reinforcing and discriminative effects of cocaine are dissociable. However, it may be possible to obtain comparable thresholds for discrimination and self-administration by refining the drug discrimination techniques employed in this research.

ACKNOWLEDGEMENTS:

Supported by NIDA contract RA-ND-93-24; NIDA grants: R01-DA-09820; R29-DA-09078; and R01-DA-06828

EVALUATING THE PHENCYCLIDINE-LIKE DISCRIMINATIVE STIMULUS EFFECTS OF IBOGAINE IN RATS AND MONKEYS

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Many drugs which share phencyclidine's (PCP) discriminative stimulus properties also displace PCP from its binding site and antagonize N-methyl-D-aspartate (NMDA) induced excitation of central neurons. Based on *in vitro* results demonstrating ibogaine's (IBO) affinity for the NMDA receptor coupled cation channels (Popik *et al.* 1994; Mach *et al.* 1995), the present study examined the PCP-like discriminative stimulus effects of IBO in rats and monkeys. Lysergic acid diethylamide (LSD), a hallucinogen without known actions at NMDA receptors, served as a reference compound. The PCP-like effects of IBO were examined in rats trained to discriminate PCP (2 mg/kg, i.p.) from saline under a 2-lever fixed-ratio (FR) 32 schedule of food reinforcement. IBO (5-20 mg/kg, i.p.) showed a complete lack of substitution, although the highest dose produced substantial reduction in response rates. IBO also failed to generalize in rhesus monkeys trained IO discriminate PCP (0.1 mg/kg, i.m.) from sham injection under a FR 50 schedule of food reinforcement. Behavioral activity was observed with higher doses (24 mk/kg, i.m.) suppressing response rates. LSD also occasioned little responding on the PCP-associated lever in either rats or monkeys. These data provide additional support for the body of evidence showing important differences between the behavioral effects of PCP and other types of hallucinogenic drugs such as LSD and IBO. In addition, no evidence was obtained in either rats or monkeys to support a hypothesis that the affinity of IBO for the PCP-site on NMDA receptors plays a major role in its acute behavioral effects.

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DIZOCIPLINE (MK801): DRUG DISCRIMINATION AND RECEPTOR BINDING STUDIES

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White Carneux pigeons were trained to discriminate 0.13 mg/kg (+)MK801 from saline under a second-order (FR10(FR5)) schedule of reinforcement, The following drugs substituted for the training drug completely (280% drug-appropriate responding) and are listed in order of potency (mol/kg): (+)MK801 > phencyclidine (PCP) > dexoxadrol = (+)N-allyl-normetazocine ((+)SKF10,047) > (±)CPP ≥ (-)SKF10,047 > N-ethyl-1,2-diphenylethylamine (CP376). (-)MK801, dextromethorphan and pentobarbital produced between 60-80% drug-appropriate responding. Morphine, *d*-amphetamine, cocaine and levoxadrol did not substitute (≤ 20% drug-appropriate responding). Displacement curves for [^{3}H]MK801 were conducted in well-washed brain (minus cerebellum) homogenates (glutamate and glycine added) from Sprague-Dawley rats and from pigeons. In rat brain, the rank order of potency was (K_i, nM): (+)MK801 > (-)MK801 > dexoxadrol > PCP > CP376 > (+)SKF10,047 > (-)SKF10,047 >> levoxadrol. Pentobarbital, (±)CPP, morphine or cocaine were without effect on [^{3}H]MK801 binding. In pigeon brain the order of potency for displacement of [^{3}H]MK801 in the 4 compounds studied was: (+)MK801 > (-)MK801 > CP376 > (-)SKF10,047. With a few exceptions, there was a good correlation between potency as a MK801-like discriminative stimuli and displacement of [^{3}H]MK801 for compounds which act as non-competitive NMDA antagonists.

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CRITICAL ROLE OF GLUTAMATE DURING OPIOID WITHDRAWAL

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To investigate the role of glutamate during opioid withdrawal, rats were continuously infused with morphine (26 nmol/µl/h) or butorphanol (26 nmol/µl/h) intracerebroventricularly (i.c.v.) via osmotic minipumps for three days. A direct i.c.v. (5 or 50 nmol/5 µl or locus coeruleus (LC; 1 or 10 nmol/5 µl) injection of glutwnate dose-dependently induced withdrawal signs in opioid-dependent animals. The withdrawal signs precipitated by glutamate were comparable to those precipitated by an opioid receptor antagonist, naloxone (i.c.v.; 48 nmol/5 µl, LC; 24 nmol/5 µl), except for the expression of some specific behaviors and the duration of withdrawal signs, The expression of withdrawal signs precipitated by glutamate or naloxone was completely blocked by pretreatment with MK-801 (an NMDA receptor antagonist; 01 mg/kg, i.p). On the other hand, glutamate or naloxone failed to precipitate any withdrawal signs in saline-treated control animals. These unique actions of glutamate in continuously opioid-infused rats suggest that a rapid release of glutamate in the LC region plays a critical role during opioid withdrawal. Furthermore, this effect may be mediated by the NMDA subtype of glutamate receptors.

ACKNOWLEDGMENTS

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THE CHANGES OF cAMP-DEPENDENT PROTEIN KINASE ACTIVITY IN THE SPINAL CORD IN THE MORPHINE DEPENDENT RATS

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The mechanisms underlying narcotic dependence remain largely unknown. The present study was to investigate the changes of cAMP-dependent protein kinase (PKA) and norepinephrine (NE) contents within the spinal cord in the morphine-dependent rats. The activity of PKA was quantified by measuring the difference of incorporation of 32p into histone (IIA) with or without cAMP. The activity was assumed to reflect PKA holoenzyme. Norepinephrine contents were analyzed by HPLC-ECD method. PKA activity decreased in spinal cord in morphine-dependent rats, showing activation of PKA in the spinal cord by systemic chronic administration of morphine. When the morphine-dependent rats treated with naloxone (2 mg/kg), the PKA activity was increased from 22±7 pmol pi /min.mg protein (n=8) to 125±18 pmol pi/min.mg protein (n=8), which is not different from that of control (110±19 pmol pi/min.mg protein, n=8). However, decrease or enhance of cAMP contents, non-difference or attenuation of NE contents in the spinal cord were observed in the morphine dependence or naloxone-precipitated withdrawal. The increase of both NE release and cAMP contents during the withdrawal are inconsistent with the changes of PKA in the spinal cord, which could not account for upregulation of cAMP pathway. These results suggested that activation or inactivation of PKA in the spinal cord play an important role in the morphine dependence and withdrawal.

DIHYDROETOKPHINE (DE) EXHIIIITS ATYPICAL PHYSICAL DEPENDENCE IN THE CHRONICALLY INFUSED RAT

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There have been a number of recent reports that dihydroetorphine (DE), a potent opiate analgesic, has little or no propensity to cause physical dependence. To evaluate this claim, DE was tested in rats that were infused chronically with the drug by the IP route. DE was examined in a substitution study, in which its ability to suppress signs of abstinence in morphine-dependent rats was assessed, as well as in a study of primary physical dependence, in which the emergence of signs of abstinence upon withdrawal from chronic treatment with DE was assessed. In the substitution study, rats were infused constantly with morphine sulfate for six days, then with DE (5, 10, 20 or 40 µg/kg/day), saline (vehicle), or morphine (positive control) for 48 hr (4-6 rats/group). During the substitution phase, body weight and behavioral signs of abstinence were recorded twice daily. Changes in body weight between groups were evaluated with the t-test, and behavioral signs of abstinence between groups were compared with the Mann-Whitney test. Behavioral signs of abstinence were suppressed by substitution of DE in a dose-related manner. In preventing weight loss associated with abstinence, all of the tested doses of DE were significantly less effective than was continuation of morphine. In the primary physical dependence study, rats were infused constantly for six days with DE on an incremental dosing schedule, such that final doses were 10, 20. and 40 µg/kg/day (4-8 rats/group). Following the DE infusion, saline was infused for four days, and data were recorded and analyzed as described above. Behavioral signs of abstinence were not significantly different from signs in rats that were undergoing concomitant withdrawal from morphine. However, all DE-withdrawn groups exhibited significantly less weight loss than the morphine-withdrawn group. In conclusion, these data suggest that DE is capable of producing physical dependence that is qualitatively similar to morphine; but the dependence is atypical in that the effects on body weight with DE abstinence or substitution are less pronounced than with morphine, while the effects on behavioral signs of abstinence arc equal to those of morphine. This could be interpreted as being indicative of a milder abstinence syndrome.

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DIHYDHOETORPHINE (DHE): AN OPIOID WITH A LOW PHYSICAL DEPENDENCE CAPACITY IN RHESUS MONKEYS

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The hypothesis that DHE, a thebaine-oripavine derivative, would have a low physical dependence capacity was based on the suggestion by Shen and Crain, (1994) that selective activation of inhibitory rather than excitatory opioid functions predicted low dependence liability. Single doses of DHE, dose-dependently substituted completely for morphine, in maximally dependent primates, at doses of 3 and 15 x 10^{-5} mg/kg, s.c. However, in a primary physical dependence study, DHE was given chronically to 5 drug-naive subjects over an 8-fold dose range, 4 to 6 times a day. Naloxone challenges, on days 16, 31, and 43, at doses up to 11 times that which would precipitate withdrawal in morphine-dependent monkeys. proved unremarkable. In addition, no withdrawal syndrome was observed during abstinence. DHE may be useful in the therapy of opioid abuse.

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ACUTE DEPENDENCE IN HUMANS; THE RELATIVE POTENCY OF NALOXONE AND NALTREXONE IN PRECIPITATED WITHDRAWAL

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The naltrexone package insert recommends a 0.8 mg s.c. naloxone challenge to detect residual opioid dependence prior to starting patients on oral naltrexone at an initial 25 mg dose. This implies that parenteral naloxone has a much greater potency than oral naltrexone for precipitating opioid withdrawal We examined the relative potency of i.m. naloxone and i.m. naltrexone for precipitating withdrawal in an acute dependence procedure chosen to simulate the sub-clinical levels of physical dependence that might be present in some patients presenting for treatment. Six non-dependent opioid-experienced volunteers were pretreated with 30 mg/70 kg i.m. morphine, and then challenged with placebo, 1, 3, or 10 mg.70 kg i.m. naloxone, or 1, 3, or 10 mg/70 kg i.m. naltrexone 24 hours after pretreatment. Mild withdrawal symptoms were observed following all active antagonist doses; 1 mg/70 kg produced less intense effects than 3 or 10 mg/kg, with the latter producing simular effects. Both peak effect and area under the curve measures showed equivalent potencies for naloxone versus naltrexone. This finding suggests that the package insert is misleading; naloxone doses higher than 0.8 mg may be needed to predict effects of 25 mg oral naltrexone, even after correcting for oral versus parenteral potencies. The apparent ceiling in precipitated withdrawal effects above 3 mg/70 kg in this study may be due to limited underlying levels of dependence. Studies conducted at higher dependence levels would be useful to extend these findings.

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EFFECTS OF DYNORPHIN ON OPIATE ADDICTION IN HUMANS

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Dynorphin A 1-13 (DYN) suppresses opiate withdrawal in rats. Its potential use in opiate dependent humans is therefore of interest. The objectives of the current study are to determine in humans the effects of various doses of DYN on opiate withdrawal, craving for opiates and safety. We conducted a between subject, double-blinded, placebo controlled study in 32 opiate dependent subjects. Subjects were maintained on morphine 15 mg IM q.i.d. for three days; 24 hours after the last dose of morphine, when mild withdrawal was present, subjects received a single i.v. bolus dose of placebo, 150, 500, or 1000 µg/kg DYN. There were no changes in blood pressure, heart rate, respiratory rate, EKG or tibia1 nerve evoked potentials throughout the study. No serious side effects were observed but numbness, itching and pins/needles symptoms were reported more frequently in the drug conditions ($p<.05$). A significant decrease on the observer withdrawal checklist was seen in the 150 and 1000 µg/kg conditions as compared to placebo ($p<.05$). On the agonist/antagonist scale, nervousness ($p<.05$), runny nose ($p<.05$), sneezing ($p<.01$), and painful joints ($p<.05$) were significantly decreased in the 500 µg/kg condition as compared to placebo. Other 'subjective measures of withdrawal, drug liking, and craving were not affected by DYN. We conclude that DYN is well tolerated and has a modest effect in reducing mild opiate withdrawal in humans. These effects were not dose related.

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DESIGN AND SYNTHESIS OF TECHNEPINE: THE FIRST IN VIVO ^{99m}TECHNETIUM SPECT PROBE WHICH LABELS THE DOPAMINE TRANSPORTER

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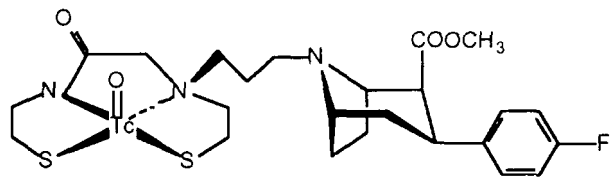
The dopamine transporter (DAT) is the binding site for cocaine and has been implicated in the addictive properties of this drug. Furthermore, DAT density has been demonstrated to change consequent to chronic cocaine abuse. The depletion of the DAT in the striatum is also a well-established marker for a number of physiological states, including Parkinson's disease (Pd). Consequently quantitative imaging of the DAT may have relevance for chronic cocaine abuse, as well as for the presymptomatic diagnosis of neurological diseases such as Pd. We now describe the design and synthesis of technepine, the first successful *receptor* based ^{99m}Tc agent which provides *in vivo* SPECT images in primates. This unique ^{99m}Tc-labeled tropane binds potently (IC_{50} = 6.0 nM) and selectively (5HT:DAT = 21; *in vivo* selectivity [striatum:cerebellum] > 4) to the DAT. Specifically, a mono amine, mono amide Tc chelating unit has been bound by a propyl tether to WIN35,428.



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EXPERIMENTAL MODEL FOR ASSESSING OPIOID EFFECTS IN VOLUNTEERS UNDERGOING OPIOID WITHDRAWAL

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The purpose of the current research was to examine a new model for assessing the ability of compounds to alleviate spontaneous withdrawal symptoms in opioid-dependent volunteers. Opioid-dependent adults resided on a clinical research ward throughout the study and were maintained on hydromorphone, orally administered daily in four 10 mg doses given at 7 am, 11 am, 5 pm, and 9 pm. For three of the six volunteers, maintenance doses of oral hydromorphone regularly administered at 5 pm and 9 pm on the day prior to testing, and at 7 am on the morning of testing were then discontinued so that volunteers experienced mild opioid withdrawal symptoms at the time of testing (i.e., 22.5 hours after the last hydromorphone dose); for the other three volunteers, only the 9 pm and 7 am doses were eliminated prior to testing (i.e, 16.5 hours after the last hydromorphone dose). Pharmacologic challenges occurred 2 times per week with at least two days separating challenges. Physiologic measures and subject- and observer-rated behavioral responses were measured before challenges and for 2.5 hr after drug administration. The current study compared the effects of butorphanol (0.375, 0.75, 1.5, 3 and 6 mg), naloxone (0.1 and 0.2 mg), hydromorphone (5 and 10 mg), and saline placebo intramuscularly administered under double-blind conditions. Six volunteers have thus far completed the protocol. Baseline measures of subject- and observer-rated withdrawal were elevated prior to pharmacologic challenge in four of the six subjects tested. The level of withdrawal in these subjects remained stable across the experimental sessions. The results indicate that subjects abstaining from maintenance on hydromorphone-substitution treatment demonstrate opioid withdrawal. In the four subjects who reported withdrawal at baseline across the ten challenge sessions, withdrawal ratings and pupil diameters were decreased by hydromorphone challenges. These results indicate that this methodology may be useful for testing the ability of compounds to alleviate spontaneous withdrawal.

SYNTHESIS AND BIOLOGICAL EVALUATION OF BRIDGED PIPERAZINE AND PIPERIDINE GBR ANALOGS

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GBR 12909 and GBR 12935 are the first reported agents to have both high affinity and selectivity for the dopamine transporter. Their promising biological properties, e.g.: slow dissociation rate, low intrinsic agonist activity for the dopamine transporter and non-stimulant profile in humans, have led us to study and develop GBR analogs as potential therapeutic agents for the treatment of cocaine abuse. In this study, we modified the piperazine moiety of GBR and synthesized several groups of bridged piperazine and piperidine GBR analogs I, II and III. The binding data for dopamine transporter (DAT) and serotonin transporter (5HTT) (labeled with [^{125}I]RTI-55) and dopamine reuptake (DAR) and serotonin reuptake (5HTR) inhibition (labeled with [^{3}H]GBR12935) show that compounds in series I generally possess high activity for both DAT binding and dopamine reuptake inhibition. The compound with R_1 as methyl, R_2 as *p*-fluorophenyl shows the highest affinity and selectivity [IC_{50} (DAT) = 8.0 nM, IC_{50} (DAR) = 9.6 nM; 5HTT/DAT = 88, 5HTR/DAR = 94]. Compounds in group II show moderate affinity and selectivity, whereas compounds in series III, hybridized structures of cocaine and GBR derivatives, show higher affinity and selectivity. Racemic III bearing N-methyl, *bis*-(*para*-fluorophenyl)methylether and a double bond has a binding affinity of 19 nM for the dopamine transporter and 188 fold selectivity for the dopamine transporter over the serotonin transporter.

NOVEL COMPOUNDS REVEAL THAT NITROGEN-BASED DRUGS ARE NOT ESSENTIAL FOR DOPAMINE TRANSPORTER BLOCKADE

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Drugs such as cocaine, methylphenidate and antidepressants that block monoamine transport are invariably nitrogen- based. The nitrogen is presumed to be necessary for anchoring the drug to the same aspartic acid residue on the transporter protein that bonds the nitrogen of a monoamine neurotransmitter. We developed a novel series of drugs which possess no nitrogen and bind to the dopamine, serotonin and norepinephrine transporters with relatively high affinity and various selectivity. In monkey striatum, O-914 bound to the dopamine transporter (IC_{50}: 10.5 ± 1.5 nM) and blocked [^{3}H]dopamine transport in cos-7 cells transiently expressing the human dopamine transporter cDNA (IC_{50}: 13 nM). This innovative series offers unique tools for modeling drug-transporter complexes and highlights the potential for developing a new generation of non-nitrogen containing drugs targeted to monoamine transporters and receptors.

ACKNOWLEDGEMENTS:

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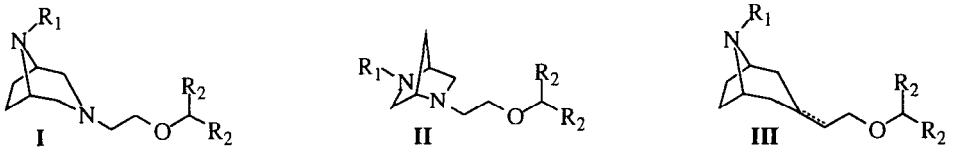

I II III

R_1=Me or 3-phenylpropyl; R_2=phenyl or *p*-fluorophenyl

MODIFIED GBR 12909 ANALOGS AS POTENTIAL AGENTS FOR THE TREATMENT OF COCAINE ABUSE.

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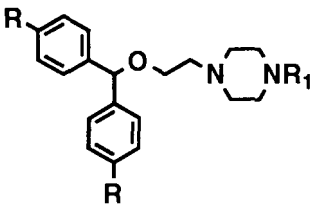
Two new series of GBR 12909 and 12935 analogs were designed, synthesized and tested for their binding affinity at the dopamine (DAT) and serotonin transporter (SERT), and for their ability to inhibit the uptake of dopamine (DA) and serotonin (5HT). In series A, analogs 8 and 12 (R=F; het=2-thienyl, 2-furyl) displayed the highest affinity for the DAT (2.2 and 1.8nM), and analogs 9 and 11 (R=H; het=2-thienyl, 2-furyl) the best selectivity for inhibiting DA uptake (281 and 300-fold with respect to 5HT). Among series B, analog 22 (R=F; R_1=2-indolylmethyl) was the most potent ligand at the DAT (Ki=0.7nM), and 21 (R=H; R_1=2-indolylmethyl) was the most selective in binding to the DAT (619 fold over SERT). In all, 38 analogs were synthesized and tested, and the binding and uptake data gave valuable new information as to the structural, electronic, and steric requirements for pharmacological activity at the DAT, and ultimately, potential use as therapeutic agents for cocaine abuse.



GBR12909; R=F; R_1=$(CH_2)_3$Ph. GBR13069; R=F; R_1=CH_2C=CHPh
GBR12935; R=H; R_1=$(CH_2)_3$Ph. GBR12783; R=H; R_1=CH_2C=CHPh
Series A; analogs 5-16. R=F,H; R_1=$(CH_2)_3$Het. or CH_2CH=CH-Het.
Series B; analogs 17-38. R=F,H; R_1=CH_2-(naphthalene, quinoline, indole, benzimidazole, benzothiophene, or benzofuran)

THE REINFORCING AND DISCRIMINATIVE STIMULUS EFFECTS OF 2ß-PROPANOYL-3ß-(4-TOLYL)-TROPANE (PTT) IN MONKEYS

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2ß-propanoyl-3ß-(4-tolyl)-tropane (KIT) is a cocaine analog that binds with high affinity and selectivity to the dopamine transporter. The purpose of these studies was to evaluate the behavioral, including reinforcing and discriminative stimulus effects of PTT in rhesus monkeys. In Exp. 1, monkeys (N=3) were trained to self-administer cocaine (0.03 and 0.1 mg/kg/inj, i.v.> under a fixed-interval (FI) 5-min schedule, during 4 hr sessions, and the effects of presession administration of PTT (0.03-0.3 mg/kg, i.v.) and cocaine (0.3-5.6 mg/kg, i.v.) were evaluated. When responding was maintained by 0.03 mg/kg/inj cocaine, PTT was approximately 10-fold more potent compared to cocaine in decreasing cocaine self-administration, with an ED_{50} value of 0.16 mg/kg compared to 1.75 mg/kg for cocaine. When 0.1 mg/kg/inj cocaine was self-administered, PTT significantly decreased cocaine-maintained responding and total session cocaine intake, with ED_{50} values of 0.12 and 0.24 mg/kg, respectively. In Exp. 2, the reinforcing effects of PTT (0.003-0.1 mg/kg/inj) were evaluated in monkeys (N=4) responding under an FI 5-min schedule of cocaine (0.03 mg/kg/inj) presentation. PTT maintained significantly lower response rates than cocaine (0.003-0.3 mg/kg/inj). In Exp. 3, the discriminative stimulus effects of PTT (0.003-0.1 mg/kg) were evaluated in monkeys (N=3) trained to discriminate cocaine (0.2 mg/kg, i.m.) from saline (0.5 ml). PTT substituted for cocaine in a dose-dependent manner and was at least 1 log-unit more potent than cocaine; these effects persisted for 8 to 24 hrs. PTT's long duration of action may be responsible for this unique behavioral profile, in which PTT shares cocaine-like discriminative stimulus effects but maintains low rates of drug-maintained responding.
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ANTAGONISM OF COCAINE'S REINFORCING EFFECTS BY AN ANTI-COCAINE MONOCLONAL ANTIBODY IN RATS

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This study evaluated the efficacy of an anti-cocaine monoclonal antibody (mAb) for modulating the reinforcing effects of cocaine. Eight male Wistar rats were progressively trained to self-administer 1 mg/kg/infusion cocaine under FR1, FR5, and then FR5:F15 min schedules of drug delivery. Cocaine delivery under the FR5:F15 min schedule maintained the highest rates of responding (2.2 responses/min), with average infusion rates of 7.5 infusion/hr and average inter-infusion-intervals of 11.4 min. Following the availability of 0.3-3.0 mg/kg/infusion doses of cocaine or saline, an inverted-U-shaped dose-response curve was generated. Beginning 24 hr after i.v. treatment with 4 mg of the anti-cocaine mAb (n=5), response and infusion rates associated with 1 mg/kg/infusion cocaine extinguished over 5 days in a saline-like pattern. Response and infusion rates returned to baseline levels in all subjects by 20 days post-treatment. After treatment with an isotype-matched control mAb (n=3), response and infusion rates remained at baseline levels. These findings are the first to demonstrate that passive transfer of an anti-cocaine mAb can reversibly antagonize the reinforcing effects of cocaine in rats using a schedule of drug delivery that resembles cocaine binge behavior in humans.

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DEVELOPMENT OF A THERAPEUTIC COCAINE VACCINE

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A therapeutic vaccine for the treatment of cocaine addicts is designed to induce anti-cocaine antibodies capable of inhibiting cocaine's reinforcing activity. A candidate vaccine was synthesized by conjugating a cocaine analog to a protein carrier. Mice immunized and boosted with the vaccine achieved high titers of anti-cocaine antibodies that were maintained for up to 6 months after the last boost. The antibodies recognized cocaine, norcocaine and cocaethylene in a competition ELISA, but displayed little or no reactivity towards benzoylecognine or ecognine methyl ester. High titer immune serum had a cocaine binding capacity of 8.5 μM, as measured by equilibrium dialysis, and contained high affinity antibodies ($4x10^7$ - $2x10^9$ M^{-1}). Immunized mice were injected i.v. with 1 mg/kg [^{3}H]cocaine. At 30 seconds, the cocaine-immune mice had significantly increased levels of cocaine in the plasmacompared to control carrier-immune mice (2025 vs 440 ng/ml, $p<0.001$, n=10). Antibody binding to cocaine led to a signficant reduction in distribution of cocaine to the brain in the immunized animals (1191 vs 2085 ng/g, p=0.003). Quantitative comparison with passive transfer of an anti-cocaine monoclonal antibody in rat self-administration studies suggests that this level of inhibition will antagonize the reinforcing properties of cocaine. The anti-cocaine antibodies did not detectably affect either the pattern of cocaine metabolism or the rate of loss of cocaine from the plasma, and cocaine administration did not reduce the level of circulating anti-cocaine antibody. Therefore, the antibodies should be able to inhibit the effects of repeated doses of cocaine. Together, these data argue that a cocaine vaccine will be a powerful new tool for the treatment of cocaine addiction.

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HEPATITIS B IN INJECTION HEROIN USERS

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This primary purpose of this study was to investigate risk factors for Hepatitis B among Injection Heroin users. Hepatitis status was known for 28 subjects; 10 were negative and 18 positive. All were male veterans in a Methadone Maintenance Treatment Program at the San Francisco VAMC. We examined differences in drug and sexual risk behaviors between negative and positive subjects. We expected Hepatitis B status to predict risk, with negative status predicting higher risk. Negative patients were matched on age, ethnicity, sexual orientation, cocaine use, combat history and marital status with Hepatitis B positive patients. All patients were positive for Hepatitis C and negative for HIV. We administered the Risk Assessment Battery (RAB) which assesses risk behavior for the last 6 months, a form of the RAB adapted for lifetime assessment and a supplementary questionnaire that investigated non-injection drug use, sexually transmitted disease and medical conditions. Hepatitis B negative patients demonstrated higher sexual risk behavior than positive patients; negative patients used condoms less frequently, reported more female sexual partners, and greater frequency of paying for sex. Access to clean needles, monogamous relationships and greater care in behavior following discovery of infection did not explain these results. No difference between groups on drug risk were found. These results do suggest that Hepatitis C spreads more readily than Hepatitis B in this population.

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TUBERCULOSIS SCREENING AT A SYRINGE EXCHANGE; FACTORS ASSOCIATED WITH RETURNING FOR SKIN TEST INTERPRETATION

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Efficient means of reaching drug users (DUs) for TB screening and preventive therapy are needed, particularly active users not in drug treatment or primary medical care. Syringe exchange programs (SEP) have the potential to deliver health interventions such as TB screening to a high risk population. We implemented a TB screening program at a New York City SEP and analyzed the acceptance of screening and factors associated with the failure to return for skin test interpretation. Participants were offered TB screening, were interviewed and received $15 at the time of skin test interpretation. From 4-1/96, of 650 exchange participants approached, 610 (94%) consented. Thirty-three percent were female, 56% nonwhite, 35% homeless, 36% without health insurance, 62% not currently in drug treatment, and 57% using syringe exchange for > = 6 months. Fifty-seven percent injected heroin, 40% cocaine. Five hundred and sixty-six (93%) returned for skin test readings and 531 (87%) completed TB screening to date. In a logistic model not being homeless (OR 2.6, 95%CI:1.2-5.6), having health insurance (OR 2.6, 95% CI:1.4-4.9) and believing HIV-related TB cannot be cured (OR 2.0, 95% CI: 1.04-3.9) were associated with not returning. Fourteen percent had > = 10 mm PPDs, 4% 5-9 mm PPDs, 73% were PPD (-), 9% anergic and 0.5% with active TB were engaged in observed therapy. TB screening can be conducted at an SEP with excellent acceptance and return rates. While measures to reduce incomplete return rates are needed, perhaps targeted towards those with particular health beliefs, SEP are an important site for TB services for active Dus, many of whom are not in drug treatment or primary medical care.

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HIV, HEPATITIS B, C AND DELTA IN A MODEL METHADONE MAINTENANCE TREATMENT CLINIC IN ISRAEL

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Parenteral drug abuse is a major predisposing factor of a variety of infectious diseases, among which viral infections, such as B, C, and delta hepatitis, and HIV are the most common. It is estimated that in Israel, 200,000 people have used illicit drugs at least once. 10,000 are considered as drug addicts - most of them use opiates. Currently, there are about 8,500 drug addicts registered in a variety of authorities, 16% of them are treated in methadone maintenance programs. The Adelson Clinic for Drug Abuse Treatment and Research at the Tel-Aviv Medical Center, uses methadone pharmacotherapy in conjunction with the overall management treatment. Since our clinic's foundation, a total of 185 patients have received at least one dose of methadone replacement treatment, with an overall retention rate of 66.3%, and a 6 months' retention of 80.5%. However, due to significant treatment policy changes adopted recently (to non-punitive counseling), the 6 months' retention rate rose up to 91.1%. At present, there are 119 patients treated in our clinic: 22 women and 97 men, with ages ranging between 21 -55 (mean 37). The methadone doses ranging between 5 mg/day (in those undergoing detoxification program) to 155mg/d (mean 105mg/d). Most of our patients were tested routinely for hepatitis B, C and delta, as well as for HIV on admission or during the early stages of treatment. We have found 4 patients out of 90 tested (4.4%) to be positive for HBsAg, 21 out of 68 patients (30.9%) had HBsAb, none previously vaccinated, 49 out of 86 (57%) were positive for hepatitis C, only one out of 83 (1.2%) was a delta hepatitis carrier, and 5 out of 102 patients (4.9%) were HIV positive. Four out of the five HIV positive patients also had antibodies to hepatitis C. In conclusion, we have found that the hepatitis and HIV prevalence among our clinic's patients is lower than in earlier reports from the USA.

DRUG USE AND HIV RISK BEHAVIORS AMONG ASIANS IN SAN FRANCISCO

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The research project identifed the patterns of drug use and HIV risk behaviors among Chinese, Filipino, and Vietnamese drug users in terms of ethnicity, gender, and immigrant status, and examined the influence of cultural factors on these behaviors. Using targeted sampling methods, we completed qualitative interviews with 104 Asian drug users in San Francisco (35 Chinese, 31 Filipino, 26 Vietnamese, 6 Japanese, and 6 other Asians and Pacific Islanders; 64% male; 63% immigrants) who were not currently in drug treatment programs. In contrast to most Asian drug users in the drug treatment programs, who had never injected drugs, 20% of the study sample were currently injecting drugs and 29% had ever shared needles. There were significant differences between ethnic groups on types of drugs at first and current use (both $p<.01$). Most Chinese and Filipino drug users started using marijuana, but cocaine or crack was the first drug for 58% of Vietnamese drug users. Most Chinese (77%) and Vietnamese (85%) drug users were currently smoking crack or cocaine. Among Filipino drug users, 45% were currently injecting or skin-popping heroin and 36% were smoking crack. Chinese and Vietnamese took drugs with the same ethnic groups or other Asians, while drug user networks among Filipinos were racially heterogeneous. Filipino drug users had been engaged in riskier behaviors than the other groups, such as having sex with IDUs, having drug using sex partners, and having sex on drugs (all $p<.01$). Asian drug users who are hidden from the street drug scene have been engaged in HIV risk behaviors. Patterns of drug use, sexual behaviors, and characteristics of social networks among Asian drug users are unique to their ethnicity, gender, and immigrant status.

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WOMEN AT RISK: PSYCHOSOCIAL RISK FACTORS AND CONDOM USE IN FEMALE IDUs

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Hypotheses: 1) A mediational model best describes the inter-relationships of family, personality, and peer risk factors, planning, and condom use. 2) Psychosocial protective factors mitigate the effects of risk factors on condom use. The sample consisted of 209 female IDUs in treatment in an AIDS or a Methadone Maintenance Clinic; half were HIV positive, and both needle sharers and non-needle sharers were present. A structured questionnaire was administered individually by ethnically-matched interviewers. Subjects were assured of confidentiality, and informed consent was obtained. Personality, family, peer, planning, and cultural factors were assessed, as well as condom use. Pearson correlations and multiple hierarchical regression analyses were used to analyze the results. The results supported the hypothesized mediational model, and the importance of psychosocial protective factors in mitigating the adverse effects of risk factors on condom use. As regards the HIV+ sample, personality attributes (e. g., risk-taking and self destructive behavior, low assertiveness, poor impluse control, and low empathy), weak mother-child and sibling bonds, and significant other needle sharing were related to little intention to use condoms and to less condom use. The findings indicated that many factors related to condom use in HIV+ subjects differed from those in HIV- subjects. The findings point to prevention and treatment strategies for reducing HIV transmission in female IDUs.

HIV INCIDENCE AMONG SYRINGE EXCHANGE PARTICIPANTS; THE INTERNATIONAL DATA

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Objective: HIV incidence among participants has typically been considered the "gold standard" for evaluating HIV prevention programs.

Methods: We analyzed data from 15 different geographic areas in which HIV incidence was either dircetly measured among syring exchange (SE) participants or could be estimated from trends in HIV seroprevalence. The studies included SE programs in Europe (Amsterdam, Lund, London, Glasgow, England and Wales), North America (Toronto, Tacoma, Portland, Montreal, New York, New Haven, Baltimore, Vancouver), Australia (Sydney and Asia (Kathmandu).

Results: Fourteen of the 16 studies showed low rates of transmission of blood-borne viruses among SE participants. With two exceptions, HIV incidence was low among SE participants (0-2/100 PYAR in low prevalence areas, 2-4/100 PYAR in moderate to high prevalence areas). In the two studies with apparent high rates of HIV incidence, potential causes include: multiple risk factors among IDUs (high injection frequencies, high sexual risk behavior, multiple social disadvantages) and SE policies that limit secondary distribution of syringes.

Conclusions: Participation in SE programs is generally associated with a low risk for incidence HIV infection. Additional research is needed to clarify the circumstances under which SE participation is not sufficient to prevent HIV infection. Issues related to implementing SEs in developing countries also need be addressed.

OTHER RISKY PRACTICES AND MODES OF HIV TRANSMISSION OF INJECTING DRUG USERS: BEYOND NEEDLES AND SYRINGES

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Miami is one of the major centers of illegal drug activity and has a significant proportion of AIDS cases among Injection Drug Users (IDUs). Since needle exchange programs are illegal and therefore do not exist in the state of Florida, other HIV prevention activities including education and counseling must play a large role in reducing the transmission of HIV among IDUs. While standard HIV counseling and prevention focus on avoiding use of contaminated needle/syringes, the present study points out additional sources of risk. The use of common paraphernalia, including cookers (containers for dissolving drugs), cottons (filters), and washwater used to rinse needle/syringes and dissolve drugs, place IDUs in additional danger of infection. Data from the NIDA-funded national and multi-site Cooperative Agreement indicate that IDUs inject frequently, averaging more than 1,000 per day, per person and that almost half of all injecting drug users (49.2%) used other risk paraphernalia (*i.e.,* cottons, cookers, washwaters) that had been used by someone else in the last 30 days. Furthermore, recent laboratory studies indicate that HIV-l might be present in contaminated cottons, cookers, and washwaters as well as in contaminated needles/syringes at shooting galleries. These findings suggest that the sharing of injection paraphernalia could be potential sources for secondary transmission of HIV-1.

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EFFECTS OF GONADECTOMY ON DISCRIMINATIVE STIMULUS PROPERTIES OF MORPHINE IN FEMALE AND MALE RATS

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Gender differences in drug addiction may reflect biological differences in sensitivity to the subjective or reinforcing properties of abused substances. We reported last year that gonadally intact female rats were more sensitive than males to the discriminative effects of morphine. The present study was conducted to determine whether these sex differences are gonadal hormone-dependent, Female and male adult, Sprague-Dawley rats were gonadectomized, and then trained to discriminate 3.0 mg/kg s.c. morphine from saline. Similar to previous results using gonadally intact rats, the ED50 for morphine substitution in gonadectomized rats was lower in females than in males (0.79 vs 1.57 mg/kg, respectively), although the time course of morphine discrimination was highly similar between the two sexes. The μ agonist, fentanyl (0.0018-0,01 mg/kg), completely substituted for morphine in both sexes, at approximately the same dose. In contrast, the partial μ agonist, buprenorphine (0.003-0.03 mg/kg), completely substituted for morphine in all females tested, but only in four of seven males. The μ agonist, U69,593 (0.056-0.18 mg/kg), did not substitute for morphine in either sex. Males were more sensitive than females to the response rate-decreasing effects of all four opioids. Naltrexone (0.01-0.1 mg/kg) dose-dependently shifted the morphine dose-effect curve to the right in both sexes, albeit to a slightly greater extent in gonadectomized females compared to gonadectomized males. The present results are highly similar to those obtained in gonadally intact rats, suggesting that sex differences in discriminative stimulus properties of morphine are not gonadal hormone-dependent in the adult rats.

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DIHYDROISTORPHINE (DHE) POTENTLY GENERATES SELF-ADMINISTRATION AND HEROIN-LIKE STIMULUS EFFECTS

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Male, Sprague-Dawley rats were trained to discriminatc 0.3 mg/kg heroin (HER) s.c. from vehicle (VEH) in a FR 10 (fixed-ratio 10), food-reinforced, operant procedure during daily (M-F), 15min experimental sessions. HER (0.03-1.0 mg/kg), morphine (MOR; 0.3-9.0), and dihydroctorphine (DHE; 10 ng/kg-560 ng/kg) were then tested for substitution for the 0.3 mg/kg heroin training dose. HER, MOR, and DHE dose-dependently produced near-100% levels of heroin-lever responding at 0.3 mg/kg, 3.0 mg/kg, and 560 ng/kg, respectively. Additionally, rhesus monkeys were trained to self-administer i.v. HER (10 µg/kg for Monkeys B, N, and H; 3 µg/kg for Monkey P) during daily, 2-h experimental sessions under FR 10 Timeout 4-min schedules. VEH and doses of HER (1-30 µg/kg), codeinc (COD; 30-1000 µg/kg), and DHE (1-100 ng/kg) were then substituted for the heroin maintenance doses. Results indicated that DHE served as a reinforcer at doses approximately >460x and >20, 000x more potent than HER and COD, respectively. These results indicate that DHE potently produces the discriminative stimulus effects of heroin in rats and is self-administered by rhesus monkeys. Given DHE's reported atypically moderate physical dependence liability in monkeys and rats (M. Aceto *et al.* & G. Patrick *et al.,* CPDD Meetings 1996), DHE appears to have all unique profile among the opiates. Supported by NIDA Contract 3-8200

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CENTRAL DISCRIMINATIVE EFFECTS OF MORPHINE (MOR) IN RATS: TRAINING VIA INTRACEREBROVENTRICULAR (ICV) ADMINISTRATION

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There have been studies of the discriminative effects of centrally administered MOR in rats trained to discriminate MOR systemically but the converse has not been done. This study was undertaken to determine the feasibility of training rats to discriminate MOR administered ICV. In rats maintained on antibiotic chow (chloramphenicol, 0.04%), MOR was delivered to the lateral ventricle one hr prior to training or testing. Rats were trained to discriminate between ICV injections of MOR (1-3 µg/3.0 µL) and saline/vehicle using a discrete-trial avoidance/escape procedure. Stimulus control was achieved within 19 (± 4.6) sessions. On generalization testing, subjects responded on the MOR-appropriate lever at ICV MOR doses equal to, and greater than, their training dose, while lower doses engendered saline-appropriate responding (ED_{50} = 0.00055 mg/kg). In contrast to the ICV training dose, MOR administered SC 30 min prior to testing engendered MOR-appropriate responding only at a dose (ED_{50} = 0.56 mg/kg) 3 orders of magnitude higher. Similarly, levorphanol (SC), but not its dextrorotatory enantiomer dextrorphan (SC; ≤ 3.0 mg/kg), produced complete MOR-appropriate responding (ED_{50} = 0.05 mg/kg). Nalthrexone (SC) produced a complete and dose-related attenuation of the effects of the training dose of MOR (ED_{50} = 0.02 mg/kg). The µ-opioid selective peptide DAMGO (ICV; ED_{50} = 0.0001 mg/kg) and the enkephalinase inhibitor SCH32615 (ICV; ED_{50} = 0.0003 mg/kg) also produced MOR-appropriate responding, while the µ-opioid selective peptide DPDPE (≤ 0.003 mg/kg) did not. These initial results indicate that the stimulus effects of ICV MOR are pharmacologically similar to those of systemic MOR. Therefore, the present methodology may be useful for investigating the stimulus effects of opioids, such as peptides, that are not behaviorally active when administered systemically.

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COMPARISON OF MESOLIMBIC SINGLE NEURONAL RESPONSES BETWEEN COCAINE AND HEROIN SELF-ADMINISTRATIONS

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The aim of this study was to elucidale the neuronal mechanisms underlying cocaine and heroin self-administration by study of the neuronal circuits involved in the self-administration behaviors. Using chronic, multi-channel, single unit recording techniques, up to 32 neurons were simultaneously recorded from medial frontal cortex and nucleus accumbens of rats trained in different sessions to self-administer cocaine and heroin. The sessions either started with cocaine and were followed by heroin self-administration, or started with heroin and were followed by cocaine self-adminstration. Self-administrations of the solution mixture with cocaine and heroin were also tested. A subpopulation of neurons in both recording areas exhibited responses both before (anticipatory responses) and after cocaine and heroin self-administration.. By comparing the neuronal activity in separate cocaine and heroin self-administration sessions, about 30 to 40 percent of neurons displayed no response in both sessions. A small percent of neurons (>20%) showed the same responses either before or after both cocaine and heroin self-administrations. A majority of neurons responded differently to cocaine and heroin self-administrations. Combining cocaine and heroin sometimes yielded different responses than observed with cocaine and heroin self-administration alone. Some anticipatory response associated with cocaine self-administration disappeared when cocaine and heroin in combination was employed, and this anticipatory response could be reinstalled by injection of naloxone (1 mg/kg i.p.). Combinations of cocaine and heroin also produce synergistic effect on post-drug infusion responses in both excitatory and inhibitory directions. This synergistic effect was effectively blocked by naloxone. The results suggest that although mesolimbic system as a whole is involved in both cocaine and heroin self-administration, separate neuronal circuits may be responsible for each drug's self-administration. The interaction between the two neuronal circuits may produce circuit activation patterns not evident when these two drugs are administered alone. Supported by DA2338.

METHADONE, LAAM AND BUPRENORPHINE: DISCRIMINATIVE STIMULUS EFFECTS IN MORPHINE-TREATED RHESUS MONKEYS

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The purpose of the current study was to compare the discriminative stimulus effects of methadone, buprenorphine, *l*-alpha-acetylmethadol(LAAM) and its metabolites in morphine-treated (3.2 mg/kg/day) monkeys (n=5) discriminating between 0.01 mg/kg of naltrexone and saline while responding under a FR schedule of stimulus-shock termination. Three hr following administration of the daily dose of morphine, monkeys responded on the saline lever, whereas monkeys responded on the naltrexone lever following either the administration of naltrexone (≥0.01 mg/kg) or the substitution of saline for the daily dose of morphine (*i.e.,* 27 hr morphine-deprived). In morphine-deprived monkeys, LAAM, nor-LAAM, dinor-LAAM, methadone and morphine reversed naltrexone lever responding. In contrast, buprenorphine partially reversed naltrexone lever responding in some monkeys and had naltrexone-like discriminative stimulus effects in other monkeys. The discriminative stimulus effects of LAAM and methadone were antagonized by naltrexone and both drugs enhanced the discriminative stimulus effects of morphine. Twenty-four hr after administration, buprenorphine (3.2 mg/kg) shifted the morphine dose-effect curve <40 fold to the right in some monkeys (those that responded predominantly on the naltrexone lever following buprenorphine alone) and shifted the naltrexone dose effect curve <40 to the right in other monkeys (those that responded predominantly on the saline lever following buprenorphine alone); both the agonist and the antagonist effects of buprenorphine were evident for < 6 days. The duration of action of these drugs was: buprenorphine>> LAAM << morphine = methadone = nor-LAAM - dinor-LAAM. This study demonstrates that methadone, LAAM and buprenorphine have dissimilar pharmacologies in non-human primates and that the effects of buprenorphine vary among subjects maintained on the same dose of morphine. These results further demonstrate that buprenorphine can attenuate some effects while enhancing other effects of opioid agonists. Finally, whether long term blockade of opioid receptors by buprenorphine will adversely affect endogenous opioid systems remains to be established.
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TASTE DISCRIMINATION OF OPIOIDS: IMPLICATIONS FOR ORAL SELF-ADMINISTRATION IN MONKEYS

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Two experiments were designed to evaluate the taste effects of several opioid compounds. First, the effect of pretreatment with the opioid antagonist naltrexone on the taste discrimination of methadone was examined, in order to block any effects of methadone which are due lo its action at opioid receptors. Three rhesus monkeys were trained to discriminate quinine from water in a two-lever, food-reinforced, operant procedure. It was established that full generalization of methadone to the quinine training concentration [0.3 mg/ml] occurred at a concentration of 0.56 mg/ml. After concentration-effect functions were determined for methadone, pretreatments of 0.1 mg/kg naltrexone were administered 30 min before the methadone test sessions. Methadone's quinine-like potency was unaffected by naltrexone, indicating that naltrexone did not antagonize this taste characteristic of methadone. Next, concentration-effect functions for morphine and levorphanol, which had similar quinine-like potencies to methadone, were compared to their non-opioid stereoisomers. By studying compounds with identical chemical structure, excepting their stereochemistry, it could be established whether the taste effects of these drugs were mediated via an opioid mechanism Both stereoisomers generalized to quinine at almost identical concentrations as their opioid counterparts, which indicates that compounds with different stereochemistry have similar quinine-like characteristics. Taken together, these experiments show that taste discrimination of opioid compounds is not mediated through opioid receptors, and is therefore likely to be independent of the oral reinforcing effects of opioid compounds. The implication of this finding is that the quinine-like characteristics of an opioid compound could be modified without altering its reinforcing effects. Supported by USPHS Grants DA-00254, DA-08568 and DA-07267.

ANTAGONISM OF RESPONSE RATE-DECREASING EFFECTS OF MEPERIDINE IN SQUIRREL MONKEYS

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The present experiment examined the response rate-decreasing effects of meperidine (MPD) using the irreversible, mu-selective opioid antagaonist ß-funaltrexamine (ß-FNA) and the competitive opioid antagonist naltrexone (NTX). Four squirrel monkeys' lever-pressing was maintained by a fixed-ratio 30 schedule of food presentation. Dose-effect curves for MPD were determined alone and in combination with ß-FNA (2.0, 4.0 and 8.0 mg/kg) and NTX (.001-1.0 mg/kg). When MPD and ß-FNA interactions were redetermined 24hr, four days, and, if the curve remained shifted, 11 and 18 days later. When MPD and NTX interactions were assessed, NTX was administered prior to experimental sessions in which the MPD dose-effect curve was redetermined. Alone, MPD dose-dependently decreased response rates. Each dose of ß-FNA for two monkeys and the highest dose for a third monkey, decreased response rates below 50% of control rates alone, and did not shift the MPD dose-effect curve or shifted it to the left. For the third monkey, 2.0 and 4.0 mg/kg ß-FNA and for the fourth monkey all doses of ß-FNA did not decrease response rates alone and shifted the MPD dose-effect curve 0.36-0.58 log unit rightward for at least four days. Doses of 0.01 and 0.1 mg/kg NTX shifted the MPD dose-effect curve 0.43 and 0.27 log unit rightward, respectively, across the four monkeys. The largest dose of NTX produced rate-decreasing effects alone, and the MPD dose-effect curve was not shifted. These data suggest that under conditions in which ß-FNA and NTX alone decrease response rates, they may not be useful tools for the analysis of rate-decreasing effects of opioid agonists. When the antagonists did not produce rate-decreasing effects alone, the rate-decreasing effects of MPD appear to be related to activity at the mu receptor. **ACKNOWLEDGEMENT:** Supported by NIDA grants DA02749 and DA00033

NOVEL BRANCHED CHAIN ALKYL ANANDAMIDE ANALOGS

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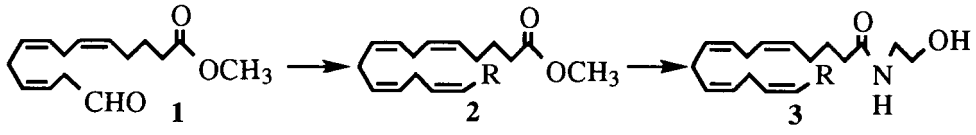
Several novel analogs **3** of anandamide (AN, R=C_5H_{11}) were synthesized where the terminal pentyl side chain (C_5H_{11}) of AN was replaced by higher alkyl, monomethylalkyl and dimethylalkyl side chains. They were synthesized from the known C_{14} aldehyde ester **1** by a Wittig reaction using the appropriate alkyl ylide. The esters **2** thus formed were converted to the corresponding AN analogs utilizing the same procedure as in the synthesis of AN. These analogs were evaluated for their binding affinity to the cannabinoid receptor (CB1) and their *in vivo* activity in the spontaneous activity and the tail flick tests. Binding studies of these novel analogs have shown that increasing the chain length and branching the chain enhances the affinity to the receptor.

ACKNOWLEDGEMENTS:

Supported by NIDA Grants DA08904, DA03672 and DA09789.



HEROIN VERSUS MONEY SELF-ADMINISTRATION BY MORPHINE-MAINTAINED HUMANS

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Five heroin-dependent subjects, maintained on divided daily morphine doses, participated in a 3 to 4 week inpatient heroin self-administration study. Each morning, subjects received a single intravenous (i.v.) injection of heroin (6.25, 12.5, 25, or 50 mg/70 kg) or placebo, and each afternoon, they had the opportunity to self-administer all, or part of, the morning sample dose. The afternoon self-administration task consisted of lo-trials under a progressive ratio schedule (PR50, 100, ..., 2800). During each trial, subjects could respond for 1/10th of the sampled heroin dose or 1/10th of -a single money value ($10, $20 or $40). The PR value increased independently for each option. The total amount of heroin and/or money chosen during the self-administration task was administered at the end of the task. Heart rate, blood pressure, pupillary diameter, and blood oxygen saturation were collected repeatedly during each session. Behavioral effects (subjective and psychomotor task performance) were assessed before and after heroin administration. Heroin produced a dose-related increase in PR break point. The dose-response curve for heroin vs. $20 was shifted to the right of the curve for heroin vs. $10. However, the dose-response curve for heroin vs. $40 did not significantly differ from the dose-response curves for heroin vs. $10 or $20. Heroin produced dose-related increases in ratings of “Good Drug Effect,” “High,” “Mellow,” and “Sedated,” and dose-related decreases in performance, pupillary diameter and blood oxygen saturation. Thus, the availability of alternative reinforcers, depending on magnitude, may be effective in reducing heroin use in opioid-dependent research subjects.

ACKNOWLEDGEMENT

Supported by NIDA grant DA09236.

MOLECULAR MODELING ANALYSES OF CANNABINOID AGONISTS AND ANTAGONISTS

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Research Triangle Institute, Research Triangle Park, NC, [+]Virginia Commonwealth University, Richmond, VA and *Organix, Inc., Woburn, MA

The identification of fatty acid ethanolamides and aminoalkylindoles (AAI's) possessing cannabinoid activity and the discovery of the cannabinoid antagonist SR-141716A has dramatically extended the structural diversity of compounds that can interact with the cannabinoid receptor. Since the three-dimensional structure of the binding site(s) for these compounds is still being investigated, we have continued to characterize the structural requirements for cannabinoid binding and activity using quantitative structure-activity relationship (QSAR) analyses. Our studies with anandamide and other fatty acid ethanolamides have indicated that reasonable pharmacophoric overlays with these compounds and classical and nonclassical cannabinoids can be obtained Furthermore, these superpositions can be obtained with energetically favorable conformations. Finally, the accurate prediction of the potency and affinity of these anandamide analogs by our QSAR model provides evidence to support the relevance of the pharmacophoric overlay and suggests that these compounds could be interacting at the same site on the cannabinoid receptor. With regard to the AAI's, we have determined that reasonable superpositions of AAI's with classical cannabinoids can also be obtained. However, the extension of the QSAR to include a range of AAI's remains problematic. In addition, Reggio et al. (personal communication) have reported that a single amino acid substitution in the cannabinoid receptor eliminates the binding of the prototype AAI, WIN-55212-2, while having no effect on the binding of anandamides or classical/nonclassical cannabinoids. Thus, any superposition of AAI's to other cannabinoid agonists remains speculative. Similarly, a reasonable superposition of the antagonist SR-141716A can be obtained, and SAR analyses are being performed to determine if this superposition is pharmacologically relevant. Supported by NIDA grant DA-0548-07

CONFORMATIONALLY RESTRICTED ANANDAMIDE ANALOGS

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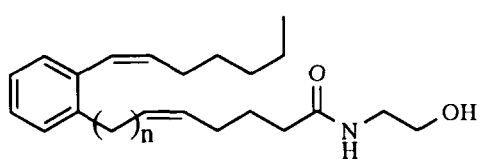
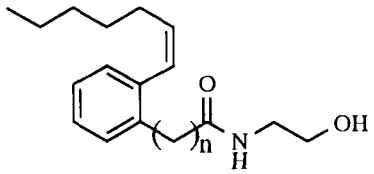
In order to address the effect of conformation on the binding of anandamide to the cannabinoid receptor, a series of conformationally restricted anandamide analogs that incorporate a phenyl ring in the arachidonyl portion of anandamide were prepared. The number of carbons in the restricted arachidonyl chain varied from 14 to 20. The arachidonic acid analogs were prepared by sequential Wittig reactions starting from commercially available bromobenzaldehydes (C_{14}, C_{16}, and C_{19} series) or bromophenethyl alcohols (C_{20} series). The first Wittig reaction installed the heptenyl side chain; the second Wittig reaction introduced the acid-containing side chain. The acid was then converted to its ethanolamide by formation of its mixed anhydride with ethyl chloroformate and treatment with ethanolamine. All three possible geometric isomers were prepared for the C_{19} and C_{20} series. For the C_{14} and C_{16} series, the ortho isomers were prepared. Preparation of the meta and para isomers is currently underway. The anandamide analogs will be assessed for cannabinoid receptor binding affinity.



n = 1: C_{20} series
n = 0: C_{19} series



n = 2: C_{16} series
n = 0: C_{14} series

SYNTHESIS, BINDING AND BIOASSAY STUDIES OF SNC 80 AND RELATED NONPEPTIDIC DELTA OPIOID RECEPTOR AGONISTS

8. N. Calderon; J. Flippen-Anderson-; H. Xu*; X. M. Becketts*; R. B. Rothman*, P. Davis§; F. Porreca§; K. C. Rice.

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Recently, we have reported the synthesis, binding and bioassay studies of the nonpeptide delta (δ) opioid agonist SNC 80 [(+)-4-[(αR)-α((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]- *N,N*-diethylbenzamide.[1] This agonist was shown to be 2000 fold more selective for δ over mu (μ) opioid receptors, in both *in vitro* and bioassays. In an effort to further characterize the chemical requirements for interaction at the δ opioid receptor, we replaced the methoxy group present in SNC 80, by a hydroxyl function, hydrogen, fluorine and iodine. We also synthesized the enantiomers and benzylic epimers of each derivative. The optically pure derivatives, were synthesized from the enantiomers of 1-allyl-*trans*-2,5-dimethylpiperazine. The enantiomers of the piperazine were obtained in >99% optical purity by optical resolution of the racemate with the camphoric acids. Since the chirality of the starting material was known and the relative configuration of one representative compound from each series was obtained by single crystal X-ray analysis, the assignment of the absolute stereochemistry of the entire series could be made. From this first series of compounds, our results showed that the fluoro and the iodo derivatives were the least selective. The compounds that retained selectivity and high affinity at the δ opioid receptor, in binding assays and potency in bioassays possessed the relative stereochemistry of SNC 80 (αR*, 2 S*, 5R*). Studies with the compounds described in the isolated mouse *vas deferens* (MVD) and guinea pig ileum (GPI) bioassays revealed that all were agonists with differing degrees of selectivity for the δ opioid receptors. Based on SNC 80 and its desmethoxy analog, we analyzed the effect of chemical modification at the *trans*-2,5-dimethylpiperazine moiety. Bioisosteric substitution by oxygen or by a methylene group of the *N*-4 of the piperazine moiety abolished the affinity of these compounds for δ and μ receptors.

[1] S. N. Calderon, *et al.,* J. Med. Chem 1994, 37, 2125

RECEPTOR-BINDING ANALYSES OF CANNABINOID AGONISTS AND ANTAGONISTS

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Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, NC

The recently identified orally-active cannabinoid receptor antagonist SR141716A was evaluated in saturation and displacement assays in F344 rat brain preparations employing our radioligand [6-^{3}H]SR141716A (^{3}H-SR). Simultaneous studies were performed with [^{3}H]CP-55,940 (^{3}H-CP) in order to compare the binding of this agonist to that of the antagonist. A group of alternatively halo-genated SR antagonist analogs were also prepared and tested along with SR141716A and cannabimi-metics comprised of D^9-THC cannabinol, cannabidiol anandamide, WIN-55,212-2, and CP-55,940 for their ability to compete for receptor labeled with either ^{3}H-SR or ^{3}H-CP. The K_D of each labeled compound was determined by Scatchard analysis, and the K_I's for the unlabeled cannabinoids were calculated using EBDA/LIGAND. The results of the Scatchard analyses were in agreement with pre-vious findings that each radioligand binds with high affinity to a homogeneous population of sat-urable binding sites. Competition studies demonstrated high affinity for the analogs with a 4'-Br or a 4'-I replacement of the chlorine on the mono chlorophenyl ring of SR141716A, comparable to that of the parent compound (in the 1 nM range). These studies also demonstrated displacement of ^{3}H-CP by all compounds with rank order potencies in agreement with previous studies. However, the significantly different K_I values obtained in competition with ^{3}H-SR suggests different modes of binding of the tritiated agonist and antagonist. This could be explained by binding at receptor subtypes or at distinct but overlapping sites on the same receptor. Expressing the data as the ratio of the K_I's from ^{3}H-CP versus ^{3}H-SR displacements (CP/SR), gives ratios <1 for known agonists and ratios of >1 for the SR compounds; an observation that serves to quantify the different binding modes. By this expression, cannabidiol shows an antagonist value >1 in agreement with earlier reports of its activity.

AN IMPROVED SYNTHESIS OF SNC 80, A HIGHLY SELECTIVE DELTA OPIOID RECEPTOR AGONIST

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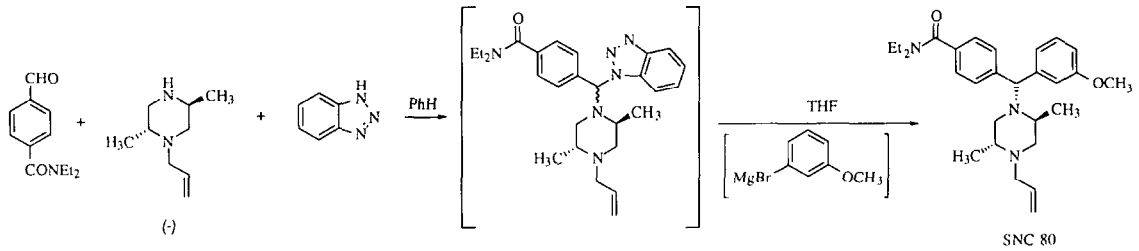
We recently described the synthesis and identification of (+)-4-[(αR)-α--((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC 80) as a highly selective, nonpeptide δ opioid receptor agonist. Further investigation of its pharmacological profile required substantially larger quantities of this compound. Our initial protocol for the synthesis of SNC 80 provided equal amounts of SNC 80 and its benzylic epimer in the last step and required optical resolution of 1-allyl-2,5-dimethylpiperazine with the camphoric acids of which only one is readily available. We have now developed a facile synthesis and resolution which provides the optically pure piperazine in 100 g quantities in the laboratory. Utilization of this material in a modification of the stereoselective synthesis of (+)-BW373U86 (Bishop and McNutt 1995) based on Katritzky's tertiary amine synthesis provided an efficient synthesis of SNC 80, which is shown below. This route is superior to our original synthesis in terms of fewer steps, higher yield and excellent diastereoselectivity. This new approach is also used to prepare new SNC 80 analogs



OPIOID PEPTIDE ANALOGS WITH A MIXED μ AGONIST/δ ANTAGONIST PROFILE

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The observation that continuous administration of δ opioid antagonists to mice or rats treated chronically with morphine greatly attenuated the development of morphine tolerance and dependence (Abdelhamid et al. 1991; Fundytus et al. 1995) suggested that opioid compounds with mixed μ agonist/δ antagonist properties may have potential as analgesics with low propensity to produce tolerance and dependence. The first mixed μ agonist/δ antagonist reported was the tetrapeptide H-Tyr-Tic-Phe-Phe-NH_2 (TIPP-NH_2; Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) which showed moderate μ agonist potency in the guinea pig ileum (GPI) assay and high δ antagonist potency in the mouse vas deferens (MVD) assay (Schiller et al. 1992). We prepared several analogs of TIPP-NH_2 containing either 2',6'-dimethyltyrosine (Dmt) or N^{α},2',6'-trimethyltyrosine (Tmt) in place of Tyr^1 and determined their *in vitro* opioid activity profiles in the GPI and MVD bioassays and in the rat brain membrane receptor binding assays. In comparison with TIPP-NH_2, H-Dmt-Tic-Phe-Phe-NH_2 (DIPP-NH_2) showed greatly increased μ agonist and δ antagonist potencies and still about 10-fold preference for δ receptors over μ receptors. Reduction of the peptide bond in the 2-3 position of the peptide sequence resulted in a pseudopeptide analog, H-Dmt-TicΨ[CH_2-NH]Phe-Phe-NH_2 (DIPP-NH_2[Ψ]), which displayed an IC50 value of 7.7 nM in the GPI assay, a K_e value of 0.5 nM against δ agonists in the MVD assay and μ and δ receptor affinities in the subnanomolar range in the binding assays (K_j^{μ}/ K_i^{δ} = 2.11). Thus, DIPP-NH_2[Ψ]] represents the first known opioid compound with balanced μ agonist/δ antagonist properties. The Trp^3-analog, H-Dmt-Tic-Trp-Phe-NH_2, also turned out to be a highly potent and balanced mixed μ agonist/δ antagonist. Replacement of Tyr^1 in TIPP-NH_2 with Tmt resulted in a compound, H-Tmt-Tic-Phe-Phe-NH_2, showing partial μ agonism in the GPI assay and potent δ antagonism in the MVD assay. Finally, the pseudopeptide H-Tmt-TicΨ[CH_2-NH]Phe-Phe-NH2 turned out to be a moderately potent μ antagonist/δ antagonist. In the mouse hot plate test DIPP-NH_2[Ψ] produced a centrally mediated analgesic effect after subcutaneous administration at a dose of 40 mg/kg. In preliminary studies using the rat tail flick test it was shown that DIPP-NH_2[Ψ] given i.c.v. was a potent analgesic which upon chronic administration at high doses produced no dependence and less acute tolerance than morphine (Fundytus et al. unpublished results).

Supported by grants from the MRC (MT-5655) and NIDA (DA-04443)

7α-CINNAMOYLAMINOORIPAVINES: POTENTIAL AFFINITY LIGANDS FOR OPIOID RECEPTORS

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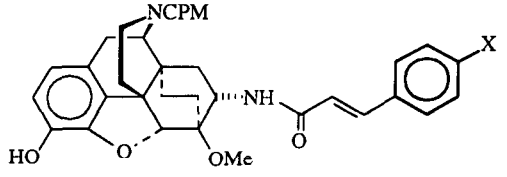
The cinnamoyl derivatives (**1-4**) of 7α-amino-N-cyclopropylmethyl-6,14-endo-ethanotetrahydronororipavine were prepared as analogs of the μ-selective irreversible antagonist clocinnamox. In the guinea pig *ileum* assay **4** was not an agonist and **1-3** showed partial agonism which could not be reversed by selective antagonists nor washed out of the tissue. In the mouse *vas deferens* assay they were non-selective antagonists. In mouse antinociceptive assays they were antagonists in tail withdrawal but only the p-methyl analog (**2**) showed evidence of irreversible (μ) antagonism. In the acetic acid-induced writhing assay (AW) **1-3** were effective though low potency agonists with differing selectivity profiles; no agonist activity could be demonstrated for **4**. In AW with 24h pretreatment 2 and 4 antagonized μ, δ and κ agonists with 2 showing substantial δ selectivity. The irreversible antagonist actions of these cinnamoyl derivatives are inferior to those of the corresponding derivatives of 14-aminomorphinone and 7α--aminomethyl-N-cyclopropylmethyl-6,14-*endo*-ethanotetrahydronororipavine.

ACKNOWLEDGEMENTS: Supported by NIDA Grant DA-00254 and NIDA Contract DA-4-8307 (to Stanford Research Institute).



(**1**) X= H
(**2**) X= Me
(**3**) X= Cl
(**4**) X= NO_2

INVESTIGATION INTO THE BINDING MECHANISMS OF THE RADIOLABELED CINNAMOYLAMINO DIHYDROCODEINONE DERIVATIVE: [^{3}H]N-CPM-CACO.

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University of Rochester, Rochester, NY and Renesselaer Polytechnic Institute, Troy, NY

N-Cyclopropylmethylnor-14B-(p-nitrocinnamoylamino)-7,8-dihydrodeinone (N-CPM-CACO) is a short-term mu-opioid agonist and a long-term antagonist of antinociception mediated by mu opioid receptors as measured in the mouse warm-water tail-flick assay. N-CPM-CACO radiolabeled with tritium in the C-8 position was used to directly determine the mechanisms responsible for the pharmacological properties of N-CPM-CACO. [^{3}H]N-CPM-CACO bound with an apparent K_d value of less than 100 pM to the mu opioid receptor in bovine striatal membranes. In competition binding experiments, the mu-preferring compounds morphine sulfate, [D-Ala^2,N(Me)Phe^4,Gly-ol]enkephalin and ß-funaltrexamine inhibited the binding of 0.5 nM [^{3}H]N-CPM-CACO to the opioid receptor by approximately 50%, while the kappa-selective compound U50,488 and the delta-selective peptide [D-Pen^2,D-Pen^5]enkephaIin had no effect. To determine if N-CPM-CACO binds covalently to the mu opioid receptor, membranes were incubated for 60 min or less at 37°C with 30 nM [^{3}H]N-CPM-CACO, denatured with sodium dodecyl sulfate and the protein precipitated by a chloroform/methanol extraction procedure. In preliminary results, the precipitated protein demonstrated covalent binding with [^{3}H]N-CPM-CACO that was time- and pH-dependent, producing optimal specific binding with an incubation of 5 min at pH 7.8. In conclusion, [^{3}H]N-CPM-CACO binds with high affinity, but also forms a covalent bond to the mu opioid receptor.

ACKNOWLEDGEMENTS: Supported by USPHS grants DA03742, DA07232 and DA06786.

OPIOID AFFINITY AND SELECTIVITY OF A SERIES OF 2-CHLOROACRYLAMIDO DERIVATIVES OF DIHYDROMORPHINONE

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University of Rochester, Rochester, NY and [B]Rensselaer Polytechnic Institute, Troy, NY

A series of 2-chloroacrylamido derivatives of dihydromorphinone was synthesized, and the affinity and selectivity of the compounds for the μ, δ, and κ opioid receptors was determined by radioreceptor binding assays using bovine striatal membranes. The 2-chloroacrylamido reactive group was added to either the 6th or the 14th position on dihydromorphinone and its N-cyclopropylmethyl (N-CPM) analog. All four compounds bound preferentially to the μ site: 6β-(2-chloroacrylamido)-4,5-epoxy-3-hydroxy-17-methylmorphinan (6-CLAMO) and its N-CPM analog (N-CPM-6-CLAMO) displayed greater affinity for the μ site than did 14β-(2-chloroacrylamido)-7,8-dihydromorphinone (14-CLAMO) or its N-CPM analog (N-CPM-14-CLAMO). Of the four compounds, only N-CPM-6-CLAMO inhibited μ binding to membranes in a concentration-dependent, wash-resistant manner at concentrations less than 20 nM. N-CPM-6-CLAMO produced minimal wash-resistant inhibition of δ and κ binding. In the mouse acetic-acid writhing test, N-CPM-6-CLAMO acted as a potent k-selective agonist. In the mouse tail-flick test, a single 1-nmol i.c.v. dose of N-CPM-6-CLAMO administered from 1 to 72 hours before testing suppressed morphine-induced antinociception, but had no effect on antinociception mediated by δ and κ receptors. Higher doses of N-CPM-6-CLAMO were required to observe short-term analgesia than were required for long-term antagonism of morphine-induced antinociception. N-CPM-6-CLAMO is a short-term κ agonist and a long-term μ antagonist.

ACKNOWLEDGEMENTS: Supported by USPHS grants DA03742 and DA06786.

COCAINE MODULATES PERIPHERAL BLOOD LYMPHOCYTE AND ENDOTHELIAL CELL CYTOKINE PRODUCTION

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Cocaine use is associated with modulation of a broad range of biological functions including the capacity to influence cytokine production by immunoeffector cells. Little is known, however, regarding the effects of cocaine on cytokine production by human peripheral blood lymphocytes (PBL) and endothelial cells. The effect of cocaine on PBL cytokine profiles and the molecular mechanisms responsible for the modulation of cytokine mRNA expression were investigated. Conditioned supematant from IL-2-stimulated PBL were evaluated by cytokine-specific ELISA (IL-4, 5, 8, 10, IFN-γ, and TGF-β) following *in vitro* cocaine exposure. Cocaine abrogated the IL-2-induced production of IFN-γ and IL-8 in a dose responsive manner. Cocaine also decreased PBL IFN-γ and IL-8 mRNA expression as determined by Northern blot and slot blot analysis. Nuclear run-on assays revealed that cocaine down-regulated the rate of IFN-γ and IL-8 transcription. In addition, because the vascular endothelium actively participates in acute and chronic inflammatory reactions and IL-8 is one of the key cytokines involved in the inflammatory process, modification of the production of IL-8 by vascular endothelial cells may interfere with host responses to infection or tissue injury. We investigated the effects of cocaine on endothelial cell IL-8 production. Conditioned supematants from an endothelial cell line were evaluated by ELISA following *in vitro* cocaine exposure. Cocaine decreased IL-8 production and mRNA expression in a dose-responsive manner. The addition of TNF-α reversed the cocaine-mediated decrement of IL-8 production in EA.hy 926 endothelial cells. Our findings suggest that the immunomodulatory effects of cocaine may be mediated, in part, by modification of cytokine production by PBL and vascular endothelial cells.

DRUG ABUSE, AIDS, HIV STRAINS, AND THE NERVOUS SYSTEM

P Shapshak; K Crandall[1]; C McCoy; W Bradley; R Fujimura; K Goodkin; C Petito; N Weatherby; SM Shah; S Delgado; RV Stewart; B Zhang; KQ Xin[2]; J Yang,' A Matthews,' M Yoshioka[3]; Z Nagano[3]; AK Srivastava[4]

Univ. of Miami Med. School, Miami, FL; [1]Brigham Young Univ, Provo, UT; [2]Yokohama City Med. School, Yokohama, Japan; [3]Tohoku Brain Inst., Sendai, Japan; [4]Walter Reed Army Inst., Washington, DC

Hypotheses. HIV-l infection and host toxic factors increase risk for central nervous system (CNS) and peripheral nervous system (PNS) dysfunction; the macrophage is at the core of neuropathology. Drug abuse increases risk for neurological dysfunction. We utilize interdisciplinary field, clinical, and laboratory studies to characterize the effects of drug abuse on behavior and HIV infection. Methods. Field: we use outreach interventions, education, risk reduction, and treatment for studies with African American Women; Lab. we use *in situ* hybridization (ISH), immunohistochemistry (IHC), and polymerase chain reaction (PCR) to detect HIV and cytokines and identify the cells involved, and DNA sequencing to characterize strains of HIV-l. Results and Discussion. Cocaine and cocaethylene perturb (inhibit) *in vitro* surface marker (CD11, CD14, CD68, and HLA-DR) expression of macrophages purified from brain using immunomagnetic beads. Activated macrophages including multinucleate giant cells are the major reservoir of HIV infection in the CNS but are rare in the PNS. However, virus load and/or virus strains may be related to CNS dysfunction and neuropathology whereas in both CNS (dementia) and PNS (neuropathy), cytokines are also involved in neuropathogenesis and may be related to apoptosis and subsequent demise of the infected individual. Conclusion. Multidisciplinary research provides a deeper understanding to defeat drug abuse and AIDS. IHC, ISH, PCR, DNA sequencing, and culture techniques provide insight into processes that may be involved in the pathogenesis of AIDS neurological disease. Drugs may be associated with additional neuropsychiatric disease. A model of neuropathogenesis is: HIV infection -> strain divergence -> macrophage/monocyte/inflammation -> toxic molecules -> -> apoptosis -> -> disease.

Acknowledgment: our work is supported by NIH grants: DA04433, DA04787, DA06227, DA06910, DA07909, DA09229, and NS26584.

ACUTE EFFECTS OF COCAINE ON CYTOKINE PROFILES IN COCAINE-DEPENDENT SUBJECTS

Zhan; X-H; E Galen; S Kang; S. Chang; R. L. Moldow; M Graves; T Newton; and M Fiala

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Cocaine-dependent individuals may be more prone to AIDS dementia following HIV-l infection compared to non-abusing, HIV-1- infected individuals. We investigated the effects of cocaine administration during experimental therapies on production of cortisol and cytokines by blood cells (Fiala *et al.* 1996). Following cocaine injection white blood cell, lymphocyte ($p < 0.05$), and T cell subset counts (N. S.) and serum cortisol levels ($p<0.05$) were increased, and PHA-stimulated lymphoproliferation ($p<0.05$) was inhibited. Mononuclear blood cells were obtained from six cocaine-dependent individuals before and after an intravenous injection of cocaine (40 mg). Post-cocaine mononuclear cells stimulated by LPS (18 hrs), produced less TNF-α,, IL-6 (N.S.) and IL-10 ($p<0.05$) compared to precocaine cells. With PHA stimulation (48 hr), IFN-γ and TNF-α (N.S.) secretion by post-cocaine cells was increased. IL-12 responses varied between patients but generally showed enhancement with PHA stimulation. In an *in vitro* model of human blood-brain barrier, IL-12 increased and IL-4 decreased the number of transmigrated mononuclear cells; TNF-α increased HIV-l penetration. These results suggest that cocaine may predispose to AIDS dementia by (a) altering cytokine balance to Thl pattern which fosters inflammation in the central nervous system, (b) increasing HIV-l penetration across the barrier, and (c) adverse effects of cortisol on the brain.

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COMBINATION THERAPY FOR MURINE RETROVIRUS USING METHIONINE ENKEPHALIN AND AZT

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Methionine enkephalin (Met-ENK 50-100 μg/ml) and AZT (1 ng/ml) were used in a combined protocol for treatment of established murine retroviral infection *in vitro*. In a model using Friend leukemia virus (FLV), AZT was able to reduce viral titers in susceptible *Mus dunni* cells while Met-ENK was not. Thus, confirming that the neuropeptide does not have direct anti-viral activity. However, Met-ENK treated spleen cells added to AZT reduced FLV replication in culture. These studies further demonstrated that Met-ENK effects were mediated via opioid receptors on lymphocytes, as activity could be inhibited by the opioid receptor antagonist naloxone. Further study suggests that this may be mediated via kappa receptors. Additionally, results indicate that, at least in part, Met-ENK effects were due to the induction of interferon gamma, which inhibited FLV replication. These studies were consistent with earlier findings that this combination of antiviral chemotherapy (AZT) and Met-ENK (as an immunostimulatory compound) could decrease morbidity and mortality due to FLV infection in BALB/c mice. The data suggest that this combination may provide benefit in human retrovirus infections.

NOVEL PENTAMIDINE ANALOGUES AS POTENTIAL ANTI-PNEUMOCYSTIS CARINII PNEUMONIA AGENTS

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Pentamidine is currently one of the drugs of choice used for the treatment of *Pneumocystis carinii* Pneumonia the most common opportunistic infection in AIDS patients and the leading cause of death in these individuals. The drug, however, is associated with a high incidence of toxic side effects. We hypothesize that the multiple pharmacological actions of the drug may be due to its conformational flexibility which allows the drug to bind to both target and non-target macromolecules. We have therefore, synthesized and tested five new piperidine-linked aromatic diimidazolines as conformationally restricted analogues of pentamidine. All five compounds significantly inhibited the growth of *Pneumocystis carinii* in a short term culture screen at 1 μg/ml. The DNA binding afftnity of these compounds were also evaluated by measuring DNA melt temperatures. The compounds showed greater affinity for poly(dA-dT) than for calf thymus DNA. The strength of the binding affinity of these compounds to poly (dA-dT) correlated with the anti-*Pneumocyslis carinii* activity. The synthesis and biological results of these compounds will be presented.

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RECEPTOR-MEDIATED ENHANCEMENT OF *IN VITRO* LYMPHOCYTE PROLIFERATION BY NOVEL d-SELECTIVE OPIOID LIGANDS

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Classical opioid receptor agonists neither enhance nor inhibit *in vitro* lymphocyte proliferation in response to Con A or antibody to the CD3/T-cell receptor complex (aCD3/TCR). However, we have shown that novel nonpeptidic d-selective opioid ligands can induce a dosedependent enhancement of *in vitro* lymphocyte proliferation. Proliferation of rat thymocytes or splenocytes was measured in the presence of Con A or aCD3/TCR, drug alone (concentrations ranging from 10^{-5} to 10^{-15} M), and drug with Con A or aCD3/TCR. Lymphocyte proliferation was unchanged compared to control when measured in the presence of drug alone. However, lymphocytes activated with Con A or aCD3/TCR and novel d-selective ligands exhibit a dose and time dependent enhancement of proliferation. We observed maximal enhancement of proliferation following lymphocyte activation, which may indicate upregulation of a receptor. Additionally, enhancement is specific, occurring with various chemical derivatives of nonpeptidic d-selective opioids but not with others. Examination of functional changes, cell surface markers of lymphocyte activation, and cytokine production as a function of novel peptidic and nonpeptidic opioids, may further delineate cellular mechanisms of *in vitro* and *in vivo* opioid mediated immunoregulation.

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BOTH μ AND κ OPIOID RECEPTORS INHIBIT ASTROCYTE GROWTH THROUGH A COMMON Ca^{2+}-DEPENDENT MECHANISM

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Morphine inhibits astrocyte proliferation by activating μ opioid receptors and by mobilizing intracellular Ca^{2+} ($[Ca^{2+}]_i$). The present study examined whether δ or κ opioid receptor activation might also mobilize Ca^{2+} and inhibit DNA synthesis. The effects of δ (DPDPE), or κ (U69,593/U50,488H) agonists were compared to PLO17 or morphine in murine astrocyte cultures at 6 days *in vitro*. μ,δ And κ-receptor expression was examined immunocytochemically (antibodies courtesy Dr. R.P. Elde). Intracellular Ca^{2+} ($[Ca^{2+}]$,) was measured using fura-2; while bromodeoxyuridine incorporation (DNA synthesis) was assessed in glial fibrillary acidic protein immunoreactive flat, polyhedral astrocytes 72 hr after drug treatment. The results show that subpopulations of astrocytes express (and/or (receptors, and their activation mobilizes $[Ca^{2+}]_i$ and inhibits DNA synthesis. Moreover, some μ- or κ· agonist-induced increases in $[Ca^{2+}]_i$ occurred in the absence of extracellular Ca^{2+}, or with nifedipine present (which blocks L-type Ca^{2+} channels); but could be blocked by thapsigargin (which depletes IP_3-sensitive Ca^{2+} stores) suggesting opioids mobilized $[Ca^{2+}]_i$· in some astrocytes. Only a few astrocytes expressed δ: receptors and δ agonists did not affect DNA synthesis. Collectively, this suggests that μ and κ receptors can suppress DNA synthesis in astrocytes through a mechanism involving Ca^{2+} mobilization. Moreover, distinct subpopulations of astrocytes express μ and ς receptors, and no single class of opioid receptor exclusively affects astrocyte growth.

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MARIJUANA USE AMONG AMERICAN INDIAN ADOLESCENTS

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Background: American Indian (AI) adolescents have been consistently found to have a higher prevalence of marijuana use than their non-Indian peers. This study examines the characteristics of marijuana users among a large sample of AI high school students. Method: Logistic regression models were developed to predict the probability marijuana use among a select sample of 1,393 AI youth who completed self-report surveys as part of the Voices of Indian Teens Project. Results: 552 (39.6%) had used marijuana at least once in the last month. Males were more likely to use marijuana at a high frequency (11 or more days over the last month) than females. Significant differences in levels of use were observed between the four AI cultural groups studied. Low frequency marijuana use (1 to 3 days over the last month) was associated with alcohol use and high frequency marijuana use was associated with the use of alcohol (males only), cocaine (males only), and stimulants (females only). When controlling for other variables in the regression equations, measures of ethnic identity, stressful life events, school performance, and psychiatric symptomatology (including antisocial behavior) were not significantly associated with marijuana use.

Conclusions: Research examining the etiology of marijuana use among AI youth should focus on its relationship to cultural factors, gender differences, and the use of other substances.

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TNFα GENERATION AND NORADRENERGIC RESPONSIVENESS IN THE CNS IN A CHRONIC POLYARTHRITIS PAIN MODEL.

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Increases in proinflammatory cytokines (e.g. TNFα) in the CNS have been intricately linked with the pathogenesis of several models of neuropathic pain. In addition, many pain syndromes that appear to have a CNS component are associated with abnormalities in autonomic activity. The present study demonstrates pain-induced alterations in TNF generation and noradrenergic responsiveness in a chronic polyarthritis pain model. Stimulation of presynaptic adrenergic receptors regulates norepinephrine (NE) release, and TNFα is among the endogenous mediators that potentially controls NE release. Initially, TNF production was found to be increased in the serum of rats which developed arthritis. When compared to rats which received complete Freund's adjuvant or normal control rats, rats with streptococcal cell wall-induced arthritis produced significantly less TNF in the peritoneum in response to LPS. In addition, $\alpha_2$adrenergic receptor regulation of that TNFα production was significantly greater in rats displaying arthritis. TNFα production was also found to be significantly increased in regions of the brain during the pathogenesis of the polyarthritic pain state. Superfusion and electrical field stimulation was applied to a series of rat hippocampal brain slices in order to study the regulation of ^{3}H-NE release. The changes in TNF generation coincided with an increase in noradrenergic output and a complete loss of TNF regulation of NE release. During the polyarthritic pain state there was a reduction of the presynaptic TNF response from inhibition of ^{3}H-NE release to no apparent regulation of ^{3}H-NE release. Understanding the interaction between CNS levels of proinflammatory cytokines and the noradrenergic nervous system will lead to an examination of mechanisms involved in treating chronic pain states with analgesic as well as nonanalgesic psychotropic drugs.

BRIEF VERSUS INTENSIVE PSYCHOTHERAPY FOR CANNABIS DEPENDENCE

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Forty long term cannabis (marijuana) users (33 males, mean age 34) seeking treatment were randomly assigned to an intensive group consisting of 16 sessions of Supportive-Expressive dynamic psychotherapy or a brief intervention group, consisting of a single therapy session containing motivational advice and a self-help manual. Subjects had to have used cannabis on a near daily basis for at least live years and have no history of other drug abuse. All subjects met the criteria for cannabis dependence according to DSM-IV. We tested the hyothesis that the brief intervention groups would be of equivalent effectiveness to the more intensive group. Data collected four months after intake indicated that 17 of the 20 in the intensive intervention had successfully quit in contrast to three in the brief intervention group. There were significant differences ($p < 0.05$) between the groups in changes on measures of cannabis use, ($F = 4.7$), psychological health-sickness ($F = 27.34$), depression ($F = 6.57$), anxiety ($F = 19.48$) and an index of severity of symptoms ($F + 8.52$), with the intensive group making large clinically significant gains over the brief group (Effect sizes (ES) of .74 vs .41, respectively, for changes in cannabis use.) Patients in the intensive group were more satisfied with their treatment, were more likely to recommend it to a friend and appeared better adjusted. Patients in the brief intervention group did succeed in cutting down their use, and reported that having the opportunity to discuss their drug use and problems with a health professional was the most helpful aspect of the treatment. This is the first report of individual psychotherapy for cannabis dependence and the results have implication for the of appropriate treatment.

EFFECT OF LABORATORY DECONTAMINATION PROCEDURES ON QUANTITATIVE DETERMINATION OF THC IN HUMAN HAIR

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External contamination of human hair specimens through environmental exposure is of concern in drug testing programs. The purpose of this study was to evaluate the effect of several simple laboratory decontamination (wash) solvents on quantitative determination of tetrahydrocannabinol (THC) in human hair. Hair was shaved from the scalp of a known cannabis user, cut into small segments, mixed and portioned into 20-mg aliquots. The mean THC concentration in hair aliquots prior to any decontamination was determined to be 250 pg/mg± 17 n =12) by GC/MS/NCI. Separate hair aliquots (N+3) were preincubated with one of two concentrations of THCd3 (1 ng/mg or 15 ng.mg) in ethanol for 30 minutes, followed by evaporation to dryness to mimic external contamination. Aliquots were than washed by vortexing for 30 sec with 1mL of one of the following solvents: methanol (ME), methylene chloride (MC), phosphate buffer (PB), isopropanol (IP), 1% SDS,dH20, or 1% SDS with dH209. Solvent was decanted and the process repeated twice for a total of three washes. Internal standard (TCHd7) was then added to washed hair, followed by overnight digestion in 1N NaOH at 37°C, extraction and GC/MS analysis. THC concentrations were reduced by the following amounts as compared to non-washed positive control aliquots: ME (84%), MC (82%), IP (74%), PB (52%), 1% SDS (70%), dH20 (38%), and 1%SHS with dH20 (82%). THCd3 concentrations were reduced by the following amounts: ME (96%), MC (95%), IP (97%), PB (63%), 1% SDS (76%), dH20 (38%) and 1%SDS with dH20 (84%). These data demonstrate that removal of external contamination and final measured THC concentration are dependent on the decontamination method.

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PROLONGED URINARY EXCRETION OF MARIJUANA METABOLITE

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Although the excretion of marijuana metabolites occurs over an extended period of time, few studies have been designed to accurately estimate excretion half-lives. We monitored excretion of the primary urinary metabolite of marijuana, 11-nor-9-carboxy-Δ9-tetrahydrocan-nabinol (THCCOOH), by GCNS in a controlled clinical study of marijuana smoking that included measurement of drug in each urine void collected over the four week study. Terminal elimination half-lives of THCCOOH were determined in six male subjects following smoking of a single 1.75% or 3.55% THC cigarette each week. Mean ± SEM half-lives calculated by the sigma minus method following the low or high dose were 31.4 ± 1.1 h (range 27.8 to 35.3) and 28.6 ± 1.5 h (range 24.9 to 34.5), respectively. The amounts of THCCOOH excreted over a seven day period were 93.9 ± 24.5 ug (range 34.6 to 171.6) and 197.6 ± 33.7 ug. Drug was detected at or above the current Federally-mandated GC/MS cutoff of 15 ng/mL THCCOOH for 33.7 ± 9.2 h (range 8 to 68.5) and 88.6 ± 9.5 h (range 57 to 122.3) for the 1.75 and 3.55% THC doses. This study documents the prolonged excretion of THCCOOH in urine and emphasizes the importance of study design in precise estimation of terminal elimination half-lives. A sensitive analytical method and a one to two week specimen collection period are important study considerations in the monitoring of marijuana excretion.

COGNITIVE AND PSYCHOMOTOR PERFORMANCE AFTER ACUTE MARIJUANA ADMINISTRATION IN HUMANS

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Marijuana has been shown to impair memory and other cognitive abilities; however, little research has focused on the effects of marijuana on reflective cognitive processing. In this study, we used the number of intrusion errors in a test of delayed recall (12 words) as a measure of reflective cognition. For a more complete performance profile, we also assessed the effect of marijuana on the digit-symbol substitution test (DSST), a measure of visual-motor coordination and response speed, and the circular lights (CL) test, a measure of gross motor coordination. Participants were 12 community volunteers (10 men, 2 women), who reported using marijuana an average of 4.7 times during the 2 weeks before the study. Each subject participated in six experimental sessions separated by at least 72 hr. At each session, subjects smoked ad lib two half-cigarettes containing either 0% or 3.58% THC. Placebo, low, and high doses consisted of 2 placebo half-cigarettes, 1 placebo and 1 active half-cigarette, and 2 active half-cigarettes, respectively. The design was a factorial crossing of three marijuana doses with two reinforcement contingency conditions. In one condition, subjects earned $.01 for every three correct responses on the performance tests, and in the other, they earned $.15 per three correct responses. Testing occurred at predrug baseline and 5 min and 2 hr postdrug (word recall) and 5, 45 min, 2, 4, IO hr postdrug (DSST and CL). Marijuana increased heart rate and subjective ratings of drug strength in a dose-related manner. High dose marijuana decreased percent correct responding on the DSST, but had no effect on the CL test. High dose marijuana also decreased the number of correctly recalled words in the delayed free recall test. There was a significant dose X reinforcement contingency interaction with respect to intrusion errors on the memory test. Under the low contingency condition, intrusion errors increased in a dose-dependent manner. However, under the high contingency condition, intrusion errors showed an inverted-U dose function, such that errors were reduced to placebo levels after high dose marijuana. These data indicate that marijuana-induced impairment in reflective cognition can be influenced by reinforcement contingency.

SR 141716A ANTAGONIZES THE DISRUPTIVE EFFECTS OF Δ^9-THC ON LEARNING IN RATS

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Responding by rats was maintained by food presentation under a repeated acquisition of behavioral chains procedure. Subjects acquired a different three-response chain each session and sequence completions were reinforced under a fixed-ratio 3 schedule. Errors produced a brief time out. Δ^9-Tetrahydrocannabinol (THC) (1-18 mg/kg i.p.) produced dose-related increases in overall percent errors and decreases in rate of responding. The cannabinoid receptor antagonist SR141716A (1-32mg/kg) had little effect on either overall percent errors or response rate when administered alone. A low dose SR141716A (1mg/kg) administered in combination with THC reversed the disruptive effects of THC across a range of doses (5.6-18 mg/kg). These findings suggest that THC produces disruptions of learning behavior in rats responding under a repeated acquisition procedure through stimulation of the CB1 receptor. The data further suggest that whereas THC can disrupt learning, the cannabinoid receptor may not play a tonically active role in learning process. Supported by DA 03573 and DA 04775.

INVESTIGATION INTO THE FUNCTION OF ENDOGENOUS CANNABINOID SYSTEMS

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Exogenously administered cannabinoids are known to produce cognitive deficits in humans as well as in laboratory animals. The presence of cannabinoid receptors as well as endogenous cannabinoids in the brain suggests the existence of a cannabinoid neurochemical system. The purpose of the present study, therefore, was to test the hypothesis that this putative neurochemical system is tonically active in cognitive processing in rats using the specific cannabinoid antagonist SR141716A (Sanofi Recherche). Two distinct types of learning and memory paradigms were employed; spatial memory was assessed in an eight-arm radial maze and a Pavolian fear conditioning procedure was used to assess freezing behavior to an auditory (80 db tone) or contextual conditioned stimulus (CS) previously paired with electric shock (1 mA intensity, 2 sec duration). SR141716A (3 mg/kg) given before either acquisition or testing failed to enhance fear conditioning to each CS. Similarly, the antagonist at a dose range from 1 to 10 mg/kg failed to enhance radial-arm choice accuracy; however, it did block the disruptive effects of Δ^9-THC (5 mg/kg), on spatial memory. The failure of SR141716A to improve performance in both tasks suggests that endogenous cannabinoid systems are not tonically involved in these cognitive processes.

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HIV, THE IMMUNE SYSTEMS, AND SELF-REPORTED SYMPTOMS OF HIV AMONG AFRICAN-AMERICAN WOMEN

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In clinical interviews and medical histories, women may mention symptoms such as swollen glands, night sweats, persistent diarrhea, unusual sores on the skin, white patches in the mouth, high fever, and purplish or brownish blotches on the legs or arms. Research is needed which relates these self-reported signs and symptoms to HIV infection and progression to AIDS among women. One hundred HIV negative (n=42) and HIV positive (n=77) African-American women who participate in prospective cohort studies at the University of Miami's Comprehensive Drug Research Center are interviewed at 6-month intervals about signs and symptoms that may be associated with HIV infection, with a current total of 277 interviews. Questionnaire items are derived from the CDC's Multicenter Study of Crack Cocaine and HIV Infection, and the Women's Interagency HIV Study. Blood samples are drawn for virologic and immunologic testing, urine samples are taken for toxicologic testing, and self-reported drug use is recorded. Three-fourths of the women use crack or powder cocaine more than once per week and, at enrollment, none use opiates. Analyses of the self-reported symptoms and their relationship to HIV infection and immune functioning indicate that the number and types of physical symptoms reported are directly related to the extent to which the immune system is compromised by HIV infection. Use of cocaine and alcohol is controlled as is AZT use among HIV positive women. The refinement of protocols for assessing self-reported signs and symptoms of HIV infection and progression to AIDS is critical for the prevention, intervention, diagnosis, and treatment of HIV and AIDS among women. ACKNOWLEDGEMENTS: This research is supported by NIDA grant DA-07909, with recruitment and follow-up through DA-06910, DA-=09229, DA-09953, NIMH grant MH-50240, and CDC grant CCU404539.

ALCOHOL AND DRUG ABUSE AMONG DOMESTIC VIOLENCE SURVIVORS AND BATTERERS

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Eighty female residents from an urban domestic violence shelter were interviewed upon entry into the facility. A structured interview was used to assess demographic information as well as patterns of alcohol and drug abuse for residents, their families, their batterers, and their batterer's families. Residents were primarily young African American and Latina women with children. Relatively few residents reported having drug or alcohol problems. However, 66.3% of the residents had a family member with a drinking problem and 63.8% of the residents had a family member with a drug problem. According to the resident reports, 43.8% of the batterers had an alcohol problem either currently or in the past and 52.5% of the batterers had either past or current drug problems. Over twenty percent of the batterers had both alcohol and drug problems. Additionally, substantial numbers of batterers used alcohol and/or drugs prior to at least one abusive incident. Half of the batterers had family members with alcohol or drug problems. The results suggest a multidisciplinary collaborative approach to the issues of domestic violence and substance abuse.

CHILDHOOD SEXUAL ASSAULT AND THE SUBSEQUENT DEVELOPMENT OF SUBSTANCE ABUSE AMONG WOMEN

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A history of childhood sexual assault (csa) has been commonly reported among women attending substance dependence and psychiatric treatment services. This quantitative study of 180 women, with a qualitative sub-group, employed a 4 group design that included: (1) women with and (2) women without a history of csa attending substance dependence treatment and (3) women with (4) and without a history of substance dependence attending csa counselling services. Regression analyses found that the hypotheses that substance use would be related to age at the time of initial assault and the relationship to the perpetrator were not supported in the direction predicted. Among women in csa treatment, those who experienced csa in adolescence by someone outside the family, were more likely to develop substance dependence than women experiencing incest in early childhood. However, women with a history of csa became intoxicated for the first time at a significantly earlier age than women without such a history, regardless of whether they later developed substance dependence. Women in substance dependence treatment with a history of csa had significantly higher somatisation and anxiety scores and were significantly more likely to have attempted suicide, self-mutilated, or self-reported eating disorder and sexual dysfunction than women in substance dependence treatment without such a history. The implications for intervention will be discussed.

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DRUG INVOLVEMENT OF WOMEN IN PROTECTIVE SERVICE JOBS

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Epidemiologic Catchment Area data indicated that women working in protective service (PS) jobs (e.g., police, security guards) might have an unusually high level of DSM-III drug disorders; e.g., PS jobs might expose women to psychosocial work environments that promote illicit drug-taking (1,2). Here, we tested whether women (or men) in PS jobs were any more or less likely to be recent illicit drug users. The data were from the National Household Surveys on Drug Abuse (NHSDA) in 1991-93, gathered by standardized self-report assessments of illicit drug use and current occupation. In total, 197 women and 730 men were in PS jobs whereas 21,414 women and 20,400 men were employed in other job categories. Post-stratification was used to hold constant macro-social determinants of drug involvement such as local street-level availability of drugs. The conditional form of multiple logistic regression was used to test our hypotheses, with a statistical adjustment for survey sampling weights, education, age, and race. These analyses showed no evidence of excess illicit drug use among PS workers, whether male or female. In comparisons of employed adults living in the same local residential areas, the estimated prevalence of illicit drug use for women and men in PS jobs was at lower than expected values, as reflected by an inverse odds ratio (OR) for PS women (OR=0.39; p=<0.001) and for PS men (OR=0.60; p<0.001), when the reference category was all other working men. An inverse association also was observed when women in PS jobs were contrasted with other working women (OR=0.59; p=0.07). If ECA findings were true, and women in PS jobs actually are more likely to be affected by drug use disorders, this is not seen in the NHSDA data on recent illicit drug-taking. These results suggest further research is needed on how work environments might affect women's health and their drug use.
(1) Anthony *et al.* JEAR 1:148-186,1992; (2) Muntaner et al. AJE 142:183-190, 1995.

RELAPSE AND COPING SKILLS OF COCAINE USING WOMEN

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Relapse in cocaine addiction is extremely common. While the general dynamics of relapse have been studied, little is known about specifics of the relapse process in women with cocaine abuse. The objectives of this study were to evaluate antecedents of relapse, patterns of relapse, and abstinence coping skills in female cocaine users. Sixty women recently abstinent from cocaine were prospectively followed for 90 days. The subjects, largely African-American (58%) single (58%) and unemployed (83%), completed a structured psychiatric interview (SCID-P SCID-II) and the Addiction Severity Index (ASI) at baseline. Current major depression (20%) and PTSD (24%) were prevalent. Subjects were administered the Minnesota Relapse and Coping Skills Questionnaire (MRCSQ) and the ASI at 30 and 90 days. Of the 60 subjects, 56 (93%) were interviewed at 30 days, and 42 (70%) at 90 days. Nineteen (32%) subjects self-reported cocaine relapses during the 90 day study period (mean time to first use 27.9 days, SD=25.5). Among these relapsers, alcohol use often preceded cocaine relapse (64%). Subjects also rated situational factors (64%) impulse to use (64%) negative emotional state (52%), interpersonal conflict (44%) and craving (44%) as important factors in relapse. Both subjects and interviewer rated negative emotional states as the most important factor in relapse, followed by interpersonal conflict and situational factors. Those who experienced only a "close call" did not differ from the relapsers on potential antecedents to relapse. Psychiatric diagnoses did not predict relapse. Abstainers statistically differed from relapsers in their use of social support ($p<.001$), avoidance of alcohol ($p<.05$), and cognitive processes of positive self-talk ($p<.05$) resolve to quit ($p<.01$) and focus on today ($p<.01$). We conclude that use of coping skills is a more important factor in the relapse process than predisposing factors. The MRCSQ promises to have both clinical and research applications.

LOCAL PERFUSION OF DYNORPHIN A_{1-17} REDUCES EXTRACELLULAR DOPAMINE LEVELS IN THE NUCLEUS ACCUMBENS

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The objective of this study was to characterize the potential role of the endogenous peptide Dynorphin A_{1-17} (Dyn A_{1-17}) in modulating dopaminergic neurotransmission in the nucleus accumbens (NAcc). Male Fischer 344 rats were acclimated for at least four days to controlled conditions. Animals were maintained on a 12 hour 1ight:dark cycle with food and water provided ad libitum. Rats were implanted stereotaxically with one guide cannula above the NAcc. A calibrated microdialysis probe was inserted through the guide cannula of each animal the night before the dialysis experiment. Artificial cerebrospinal fluid (aCSF) was delivered by pump at a constant rate of 1 ul/min. On the day of the experiment six 20 min. baseline samples were taken. Half the animals received a 20 min. perfusion of Dyn A_{1-17} after which nine samples were taken at 20 min. intervals, followed by perfusion of aCSF with nine samples taken. The other animals received aCSF, then Dyn A_{1-17} in a counterbalance design. Therefore, each animal served as its own control. Dialysate samples were assayed for dopamine (DA) by HPLC-EC detection. Data analysis show that DA levels were lower [$F(1,6) = 45.28$] after the perfusion of Dyn A_{1-17} when compared to aCSF perfusion. Conclusion: The observed modulation of dopamine by Dyn A_{1-17} gives new insight into the neurobiology of cocaine's effects and could be useful in the design of pharmacotherapeutic agents.

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EFFECT OF THE KAPPA OPIOID AGONIST EKC ON COCAINE AND FOOD SELF-ADMINISTRATION IN RHESUS MONKEYS

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Four rhesus monkeys were trained to self-administer 0.032 mg/kg/inj cocaine (i.v.) and 1 gm food pellets during alternating daily sessions of cocaine and food availability. Following initial determination of the cocaine dose-effect curve, we examined the effects of chronic treatment with saline and the kappa opioid agonist ethylketocyclazocine (EKC) on self-administration of food and two unit doses of cocaine (0.01 and 0.032 mg/kg/inj) at the peak of the ascending limb of the cocaine dose-effect curve. Each treatment was in effect for ten consecutive days. During saline treatment, monkeys usually self-administered the maximum number of food pellets and cocaine injections. Continuous infusion of EKC (0.0032-0.032 mg/kg/hr) produced a dose-dependent, statistically significant and naloxone-reversible decrease in the self-administration of both 0.01 and 0.032 mg/kg/inj cocaine without significantly altering rates of food self-administration. These selective, EKC-induced decreases in cocaine self-administration were usually sustained throughout the 10-day treatment period. The diurnal patterns of cocaine self-administration during treatment with 0.032 mg/kg/hr EKC resembled the diurnal patterns of self-administration produced by substitution of saline for cocaine. Thus, these results are consistent with the conclusion that EKC decreased the reinforcing effects of cocaine. In addition to decreasing rates of cocaine self-administration, EKC also produced emesis in one monkey and sedative effects in all monkeys. However, tolerance developed rapidly to the emetic and sedative effects of EKC. These results indicate that at least some kappa opioid agonists may produce selective decreases in cocaine self-administration in rhesus monkeys while producing only transient and mild side effects. Additional kappa agonists are currently being evaluated. Supported in part by grants DA02519, DA04059 and DA00101 from NIDA, NIH.

EFFECTS OF "BINGE" COCAINE ON D_1 AND D_2 DOPAMINE RECEPTORS IN RAT BRAIN AS MEASURED BY PET

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The present study investigated the effects of acute and chronic "binge" cocaine administration on the *in vivo* binding for [^{11}C]SCH23390 and [^{11}C]N-methylspiperone at D_1 and D_2 dopamine receptors respectively, using a high resolution positron emission tomography (PET, Hamamatsu SHR-2000). Adult male Sprague-Dawley rats were injected with saline or cocaine HCl (15 mg/kg) three times daily at 1-hr intervals to approximate the pattern in which cocaine is often abused by humans. PET scans were performed for D_1 and D_2 dopamine receptors at one hour and 3.5 hours following the last cocaine injection, respectively. Dopamine D_1 and D_2 receptors binding was quantified using a three compartment analysis and graphical analysis methods respectively. No significant change in the *in vivo* binding for either ligand was found in the acute (two days) "binge" cocaine treatment. A significant decrease in the binding potentials of [^{11}C]SCH23390 was found in the striatum after seven ($p<0.05$) and 14 ($p<0.01$) days of "binge" cocaine treatment. A significant decrease of [^{11}C]N-methylspiperone binding was found in the striatum only after 14 (<0.01) days of cocaine treatment. Saturation experiments with various amounts of each carrier ligand indicated that the observed alterations of *in vivo* binding were mainly due to apparent alterations in the affinity, not in the number, of binding sites. The results of this *in vivo* study may have important implication for the development of pharmacotherapies in human cocaine abusers.

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STIMULATION OF THE PRODUCTION OF cAMP BY DOPAMINE D_1 RECEPTOR AGONISTS IN RHESUS MONKEY AND RAT STRIATA

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The reinforcing effects of psychomotor stimulants appear to be mediated by the dopaminergic neurotransmitter system. Dopaminergic signal transduction has been studied extensively in the rodent brain; however, comparatively little research has been conducted using primate brain. Comparisons between rodents and primates have shown species differences in the ability of dopamine (DA) D_1 receptor agonists to stimulate the production of cAMP. The present study compared the efficacy of six phenyl-benzazepine D1 receptor agonists in striatal homogenates of rats and rhesus monkeys. Tissue was homogenized (10mM imidazole HCl, 2mM EGTA) at dissection and frozen prior to assay. Production of cAMP was stimulated in 10mM imidazole HCl, 10mM theophylline, 6mM MgSO4, 600µM EGTA, 1.5mM ATP and 10µM GTP. [3H]cAMP displaced from a bovine adrenal protein was used to determine the amount of cAMP produced. Only SKF 38393 had a difference in efficacy between species. The relationship between me cAMP efficacy and the behavioral effects of D1 agonists in rats is unclear. However, in rhesus monkeys the cAMP efficacy of a D1 agonist predicts its ability to function as a reinforcer. For example, the D1 agonists with higher efficacies, SKF 81297, SKF 82958 and R(+) 6-BrAPB, functioned as reinforcers in rhesus monkeys, but SKF 38393, SKF 77434, and S(-) 6-BrAPB, which have lower efficacies, did not (Weed and Woolverton, 1995, JPET 275(3): 1367-1374).

Agonist	Rhesus	Rat	Agonist	Rhesus	Rat
SKF 81297	96.3% (17.8)	101.2% (11.1)	SKF 38393	32.5% (15.6)	71.7% (5.6)
SKF 82958	82.1% (13.3)	93.3% (11.8)	SKF 77434	31.6% (17.3)	42.1% (8.3)
R(+) 6-BrAPB	59.1% (14.0)	69.9% (8.2)	S(-) 6-BrAPB	15.9% (16.4)	11.6% (6.0)
	% of 100µM DA (± SEM)			% of 100µM DA (± SEM)	

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DOPAMINE D_3 RECEPTOR AGONISTS PARTIALLY REPRODUCE THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE IN MONKEYS

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Dopamine (DA) agonists and antagonists varying in affinity and selectivity at the D_3 vs. D_2 receptor subtypes were studied in squirrel monkeys trained to discriminate cocaine from vehicle using a two-lever choice procedure. All DA agonists engendered dose-related increases in the percentage of cocaine-lever responses, reaching average maximums of 61 - 85% at doses that decreased me response rate. The order of potency for engendering cocaine-lever responding (PHNO > NPA > 7-OH-DPAT > PD 128,907 > quinpirole > bromocriptine) approximated the reported order of potency of the drugs for stimulating mitogenesis and for inhibiting [^{125}I]iodosu1piride binding in cells expressing cloned human D_3 receptors, but not D_2 receptors. The cocaine-like stimulus effects of the preferential D_3 agonist PD 128,907 were attenuated by DA receptor antagonists with an order of potency (nemonapride > eticlopride > YM-43611) that corresponded more closely to their reported order of affinity at cloned D_3 than D_2 receptors. The cocaine- like stimulus effects of 7-OH-DPAT also were attenuated by eticlopride, whereas the effects of neither PD 128,907 nor 7-OH-DPAT were attenuated by the D_1 receptor antagonist SCH 39166. In a final series of experiments, the discriminative stimulus effects of cocaine were enhanced in an additive manner by PD 128,907, 7-OH-DPAT and quinpirole. The results support a role for D_3 receptor mechanisms in the cocaine-like stimulus effects of D_3-preferring agonists and suggest that similar mechanisms may contribute to the subjective effects of cocaine.

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EFFECT OF CHRONIC AND ACUTE IV COCAINE ON ESTRUS CYCLICITY AND D3 RECEPTOR DENSITY IN FEMALE RATS.

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The present study examined the effect of chronic and acute IV cocaine administration (3.0 mg/kg) on D3 receptor density in the striatum and nucleus accumbens. Female Sprague-Dawley rats (n=22) were fitted with a subcutaneous vascular access port (Mactutus et al. 1994) and allowed to recover for three days. Administration of IV cocaine was either chronic (14 X 1 daily) administration or acute (13 X 1 daily saline, cocaine challenge on day 14). There was no effect of either chronic or acute injections on estrus cyclicity (mean length of estrus = 4.44±0.09 days). Dopamine D3 receptor density was determined by saturation analysis using [3H](+)-7-OH-DPAT (0.1-10 nM; Wallace and Booze 1995). Labeling of D3 receptors was performed in the presence of 10 mM Gpp(NH)p to prevent [^{3}H](+)-7-OH-DPAT binding to D2 receptors. Preliminary analyses indicate that D3 receptor density was reduced 22% in animals chronically treated with cocaine, compared to the acute group. A similar trend was also observed in the nucleus accumbens from animals chronically treated with IV cocaine, suggesting a down-regulation in the density of D3 receptors. Collectively, these data suggest that chronic, but not acute, IV cocaine administration produces alterations in the dopaminergic system by reducing the density of presynaptic D3 receptors.

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FUNCTIONAL MRI DETECTION OF CEREBRAL BLOOD VOLUME REDUCTION IN HUMANS AFTER INTRAVENOUS COCAINE

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Cocaine has been shown to alter cerebral perfusion. This study used functional MRI, which offers high spatial/temporal resolution, to detect the acute effects of cocaine on cerebral blood volume (CBV). Subjects were nine males aged 31±2 years (mean±SE) reporting casual cocaine use (15±5 lifetime exposures), who tested negative for recent alcohol/drug exposure. Magnetic resonance imaging was conducted on a 1.5 Tesla G.E. Signa scanner, retrofit with a whole body echo planar imaging coil. CBV was determined in an axial whole brain slice positioned above the lateral ventricles and parallel to the orbitomeatal line A steady-state dynamic susceptibility contrast MRI method was used to measure relative CBV. Using this method, which avoids artifacts produced by multiple injections of contrast agent, subjects were injected with four boluses of gadoteridol (0.075 mmol/kg) via an antecubital vein catheter and baseline CBV was determined from the area under the third bolus curve. Cocaine (0.4 mg/kg, i.v.) was then administered as a slow push over one minute and CBV was measured 10 minutes later. Cocaine significantly increased pulse rate (+49%), blood pressure (+20%) and subjective "high", "euphoria", and "craving" ratings ($P<0.02$). Cocaine significantly reduced CBV by 20±5% ($P<0.006$), while contrast arrival and mean transit times (measures of blood flow velocity) were earlier and shorter, respectively ($P<0.0005$). These findings suggest that cocaine reduces CBV while it increases blood flow velocity and further document the vasoactive properties of cocaine.
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CEREBRAL BLOOD FLOW RESPONSE TO IV COCAINE IN HUMANS: QUANTITATIVE XENON-133-SPECT STUDIES

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Objective To develop a procedure for rapid, repeated determination of regional cerebral blood flow (rCBF) in humans during a pharmacologic challenge. This pilot study was designed to assess the value of quantitative blood flow imaging in modeling the effects of cocaine on regional brian activity in relation to its subjective effects over time. ***Methods*** Subjects were chronic cocaine users, non-opiate-dependent and experienced in laboratory studies of the behavioral effects of repeated doses of IV cocaine. Each subject was studied on two separate days in a counterbalanced design- placebo, versus 32mg/70kg cocaine. This dynamic SPECT technique gives absolute rCBF averaged over four minutes at each time point. On each day, subjects were scanned three times: at rest, prior to a dose of drug or placebo, and then again at four and eighteen minutes after-- a pharmacologic activation study. Subjective effects were recorded immediately prior to each scan with our standard VAS and ARCI battery ***Results*** Initial ROI (region-of-interest) analyses of six subjects show a biphasic response over time after a dose of cocaine which varies significantly across regions. Blood flow increases uniformly by 10% at the earliest timepoint after cocaine (4-8 minutes) and decreases variably by 15-20% below baseline measures at the later time (18-22 minutes), while subjective effects are already waning. The largest decreases were seen consistently in the cerebellum(17-20%), followed by the left hemisphere (8-12%), and smallest in the right hemisphere (3-5%). Interestingly, placebo doses induce similar increases early, but less substantial decreases later, indicating the possibility that conditioned responses to passive cocaine doses exist at the level of rCBF. These results are consistent with recent studies in mammals by other groups demonstrating acute increases in cerebrovascular resistance after IV cocaine followed by significant decreases below baseline levels. This study demonstrates the value of quantitative rCBF-SPECT in evaluating the complex effects of cocaine on brain function.

PROTON MRS OF HUMAN BASAL GANGLIA AFTER INTRAVENOUS COCAINE ADMINISTRATION

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Proton magnetic resonance spectroscopy (^{1}H MRS) was used to evaluate changes in basal ganglia metabolite levels after intravenous cocaine administration. Subjects were 27 males aged 28±5 years (mean±SD) reporting casual cocaine use (13±14) lifetime exposures), who tested negative for recent alcohol/drug exposure. Studies were perfomed on a 1.5 Tesla G. E. Signa scanner. PRESS localization was use to acquire ^{1}H MRS signals from 8 cm^3 cubic volume centered in the basal ganglia which contains high densities of cocaine receptors. Unsuppressed water spectra and suppressed spectra containing resonances for cytosolic N-acetyl-aspartate (NAA), total creatine (Cr), choline-containing compounds (Cho) and myo-inositol (Ino) were obtained at 5 minute intervals at baseline and after intravenous one-minute infusions of placebo (n=7), 0.2 mg/kg cociane dependent manner ($P<0.01$), while the water signal intensity was unchanged. Cocaine also increased the signal intensity of all cytosolic resonances in a dose dependent manner. The increase in the NAA resonance was statistically significant ($P<0.01$) and that of Cho was nearly significant ($P=0.051$). These water and metabolite resonance changes may be indicative of cellular ion imbalance and cell swelling that could be secondary to inhibition of the Na^+/K^+-ATPase. ACKNOWLEDGEMENTS: Supported by NIDA grants DA09448, DA04059, Da00064 and DA00115.

ALTERATIONS IN BRAIN CHEMISTRY OF COCAINE ABUSERS STUDIED USING ^{1}H MAGNETIC RESONANCE SPECTROSCOPY

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Chronic cocaine usage and withdrawal in humans has been associated with such neurotoxic effects as psychoses, altered glucose metabolism and frontal lobe hypoperfusion. Recent advances in *in vivo* magnetic resonance spectroscopy (MRS) allow us to noninvasively assay key molecules involved in brain metabolism in humans. Cocaine dependent subjects (n=14) and age-matched controls (n=12) were recruited from the general population. Following a screening procedure, subjects in the cocaine group received a predrug spectral scan using a 0.5 Tesla GE Signa scanner. Spectra were obtained from the left basal ganglia and frontal cortex using a 4" surface coil with single voxel localization. Several chemical spectra differed significantly in the cocaine group when compared to the control group. Most notably, the ratio of N-acetylaspartate (NAA) to creatine (Cr) containing compounds was decreased in both areas. Twenty four hours later, subjects received three doses of cocaine (10, 20 and 40 mg iv) followed by a second MR spectral acquisition. The reduction in NAA/Cr ratio was partially reversed in frontal cortex after cocaine administration. The ratio of choline containing compounds to Cr was also reduced with respect to controls in the frontal cortex after cocaine injection. These results suggest that chronic cocaine use may be associated with neurochemical abnormalities that are responsive to acute cocaine administration.

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ACTIVATION OF LIMBIC REGIONS DURING CUE-INDUCED COCAINE CRAVING

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Cocaine-related cues can be used to reliably evoke drug craving under controlled laboratory conditions. We have applied this finding in the brain imaging setting to help identify which brain structures are differentially activated during cocaine craving. Preclinical research has demonstrated that cues which signal cocaine or other natural rewards can produce increased dopamine release in mesolimbic brain regions. We measured potential limbic activation during cue-induced craving in human patients by monitoring rCBF (regional cerebral blood flow). rCBF was imaged in abstinent cocaine patients (n=14) and in controls without a cocaine use history (n=6). The single imaging session featured 1) 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 co-registered with an MRI (magnetic resonance image) to permit anatomical localization of radioactivity. Cocaine patients showed reliable rCBF increases in amygdala, anterior cingulate and temporal pole during the cocaine video, while caudate rCBF decreased. Controls did not show this pattern. Neither group showed differential increases in non-limbic comparison regions. Results suggest limbic activation may be one component of cue-induced craving.

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CORRELATION OF CUE-ELICITED COCAINE CRAVING WITH METABOLIC ACTIVATION IN PREFRONTAL CORTEX AND MEDIAL TEMPORAL LOBE

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Environmental stimuli that are regularly associated with drug use are thought to elicit behavioral and physiological responses that contribute to drug craving and, thereby, to the perpetuation of addiction. As curbing craving for cocaine has been identified as potential target for therapeutic intervention, knowledge of the brain mechanisms that underlie craving is needed. In order to elucidate these mechanisms in human subjects, measurements of regional cerebral metabolic rates for glucose (rCMRglc) using the [F-18]fluorodeoxyglucose method and positron emission tomography were paired with self-report assessments in cocaine abusers during two experimental sessions. Testing involved presentation of a neutral videotape on arts and crafts during the first test session and a cocaine-related stimulus complex (videotape of cocaine-related activity and paraphernalia; presence of paraphernalia and a small amount of cocaine) during the second. In 13 subjects with a history of cocaine abuse, but not in five normal controls, rCMRglc in visual association areas and in cortical regions implicated in working and episodic memory was increased during the presentation of cocaine-related cues compared to values obtained when neutral cues were presented. Increases in the amygdala and the dorsolateral prefrontal cortex, brain areas implicated in emotional and working memory respectively, were correlated with self-reports of cocaine craving. The findings indicate that a distributed neuroanatomical network related to the memory processing may link exposure to relevant environmental cues with the genesis of cocaine craving.

CHANGES IN BRAIN PERFUSION DURING OPIOID DEPENDENCE: SPECT IMAGING WITH Tc-99M-HMPAO

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The aim of this study was to describe abnormalities in brain perfusion in pure opioid dependent patients (DSM-IV 304.00). Twenty-one opioid dependent patients were included and Tc-99m-hexamethyl-propylene-oxime (Tc-99m-HMPAO) brain single photon emission computed tomography (SPECT) was performed to evaluate regional cerebral blood flow (rCBF). Cerebral computed tomography (CCT) was administered to seventeen patients in order to assess the possible effects of substance abuse on brain morphology. Drug history was evaluated with Europe-Addiction Severity Index (ASI). Present drug consumption was screened by urine samples with EMIT. Thirteen patients were undergoing a detoxification treatment and eight patients a methadone maintenance program. Just before imaging all subjects were examined in order to detect withdrawal symptoms with Wang's withdrawal scale. No subject showed withdrawal symptoms. Normalized rCBF-values in corresponding regions of interest (RIO) in both hemispheres were compared. Significantly higher left sided rCBF-values were found in the pre- and postcentral gyre ($p=0.001$), the mesiotemporal ($p=0.003$), superior temporal ($p=0.003$) and inferior parietal cortex ($p=0.007$). This study shows changes in brain perfusion during opiate dependence.

IMAGERY AND PET IMAGING OF CRAVING EXPERIENCES IN ABSTINENT OPIATE ADDICTS

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Craving is a major factor in addiction, predicting poor outcome to treatment. In order to better understand the brain mechanisms of craving we have developed an imagery-based procedure using personal scripts of craving in abstinent opiate addicts. Six subjects were required to imagine and describe their craving experiences while autonomic measures of heart rate and mean arterial pressure were taken. A significant increase in mean arterial blood pressure while describing drug craving compared with neutral descriptions was observed in all subjects. These results provide preliminary evidence that the active imagery technique together with autonomic measures is a useful tool in the assessment of craving for opiates. We are now using this procedure in order to explore the brain substrates for craving using 15-O water as the blood flow tracer in PET scans. Subjects are scanned whilst they listen to their own scripts of craving and neutral descriptions, with each repeated six times. So far two patients have been successfully studied, their data and those from a further four to be completed will be presented at the meeting.

OPIOID RECEPTOR BINDING IN METHADONE MAINTAINED FORMER HEROIN ADDICTS BY PET [IMAGING] USING [^{18}F]CYCLOFOXY

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We have studied opioid receptor binding by PET imaging using [^{18}F] cyclofoxy, in 13 long term, stabilized methadone maintained patients (MMP) with no on-going drug abuse and in 11 healthy control subjects (CS). The MMP were stabilized on daily maintenance doses ranging from 30 - 90 mg/day. MMP were characterized with respect to medical, psychiatric and drug abuse history, as well as with respect to neuroendocrine status at the Rockefeller University Hospital; they were then studied with PET imaging (Scanditronix 2048-15B) at the NIH Clinical Center. These findings concur with findings of other studies, that normalization of most aspects of physiology and behavior occur during clinically effective treatment with methadone. After correcting data from all scan slices in each subject for movement of head, no laterality of significance was found for any single brain region in either study group. The six brain regions selected in advance of this study, because of the greatest interest for addictive disease and pain research, were subsequently found to be the areas of most extensive mu (kappa) opioid receptor binding: thalamus, amygdala, caudate, insula, anterior cingulate and putamen, in descending order for total and specific binding. Specific binding was reduced from 23% to 35% in the six brain regions in methadone maintained former heroin addicts studied 22 hours after the last oral dose of methadone (Group F [1,22] = 18.27, $p<0.0005$). Over 65% of mu (kappa) opioid receptors were found to be available for opioid ligand binding in methadone maintained patients. (Supported in part by DA-P50-05180, DA00049 and M01-RR00102)

FLUMAZENIL ANTAGONIZES THE DISCRIMINATIVE STIMULUS EFFECTS OF TRIAZOLAM IN HUMANS

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Human subjects were trained to discriminate triazolam (0.35 mg/70 kg) from placebo under a standard two-response drug discrimination procedure. Testing was conducted in a counterbalanced design under a two-response and a novel-response procedure, in which subjects were told to respond on a novel-response alternative if they received a drug unlike either training stimulus. During each testing session, subjects received capsules containing 0, 0.35 or 0.56 mg/70 kg triazolam. Forty-five minutes after capsule ingestion, either increasing doses of IV flumazenil (0, 0.15, 0.45 and 1.05, mg/70 kg) or successive placebo doses were administered. Thus far, preliminary results have been obtained under the two-response procedure in two subjects. When 0.56 mg/70 kg triazolam was followed by placebo IV administrations, 100% triazolam-appropriate responding was occasioned and self-reports of sedation were increased compared to baseline in both subjects. When 0.56 mg/70 kg triazolam was followed by increasing doses of flumazenil, responding shifted from 100% triazolam-appropriate at the lower doses of flumazenil (0, 0.15 mg/70 kg) to 100% placebo-appropriate at the higher doses of flumazenil (0.45, 1.05 mg/70 kg) in both subjects. Similarly, on these sessions, self-report ratings of sedation decreased as the dose of flumazenil increased. These preliminary results indicate that the discriminative and self-reported effects of triazolam are antagonized by flumazenil in human triazolam discriminators.

ANTICONFLICT ACTIVITY OF DIAZEPAM IN RATS TRAINED TO DISCRIMINATE DIAZEPAM FROM VEHICLE

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Benzodiazepines such as diazepam produce both therapeutic effects (antianxiety effects) and unwanted side effects (intoxication). In the present study, an animal model was developed that allowed examination of diazepam-like discriminative stimulus and anticonflict effects of a drug in the same rats during a single session. Rats, trained to discriminate diazepam (5 mg/kg, i.p.) from vehicle in a 2-lever drug discrimination procedure, were subsequently trained to press a third lever under a multiple FI (60 sec) FR5+shock schedule of food presentation. Diazepam (0.75-10 mg/kg) produced dose-dependent substitution for the training dose in all rats; however, it produced anticonflict effects in only five of the eight rats. In four of these five rats, diazepam slightly increased punished responding at a dose that produced predominantly vehicle-lever responding, although an additional increase in punished responding was observed at higher doses that produced responding mainly on the diazepam lever. These results demonstrate the potential utility of a new method to directly compare the anxiolytic and discriminative stimulus effects of drugs.

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EFFECTS OF ZOLPIDEM AND TRIAZOLAM ON HUMAN PSYCHOMOTOR AND COGNITIVE PERFORMANCE

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Zolpidem (ZOL) is an imidazopyridine hypnotic with selective affinity for a subclass of the benzodiazepine (BZ_1) receptor. Human laboratory studies comparing ZOL with the benzodiazepine hypnotics suggest similar psychomotor and cognitive performance profiles for the two classes of hypnotics. The present double-blind, placebo-controlled, crossover study evaluated the effects of orally administered ZOL (5, 10, 20mg/70kg) and the benzodiazepine hypnotic, triazolam (TRZ; 0.125, 0.25, 0.5mg/70kg) on psychomotor performance (circular lights and the digit symbol substitution test - DSST) and cognition (word recall, digit entry and recall, time estimation and a computerized version of the Trail-Making Test) in normal human subjects (N = 11). ZOL and TRZ produced comparable decrements in performance on the circular lights and DSST tasks. Relative to placebo, both drugs significantly impaired recall of a word list presented after drug administration and had a tendency to enhance recall of a comparable word list presented before drug administration. On measures of temporal estimation, TRZ (0.5mg/70kg), but not ZOL, increased estimates of a 5 sec. period and decreased estimates of an 80 sec. period. While both ZOL and TRZ impaired general performance on the Trails-B task (total time of completion), there were significant drug interactions on other measures of Trails-B performance: ZOL, but not TRZ increased the number of target and sequence errors, and total length of the trail. These findings demonstrate a unique psychomotor and cognitive performance profile for zolpidem in human subjects.

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ABUSE LIABILITY OF FLUNITRAZEPAM AND TRIAZOLAM IN METHADONE MAINTENANCE PATIENTS

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Benzodiazepines (BZD) are frequently abused by opioid-dependent and methadone-maintenance patients (MP). In Spain, as well as in other countries, flunitrazepam (FNZ) is the most frequently abused BZD. When MMP were asked about their liking about different BZD, FNZ obtained the highest score. In healthy volunteers, FNZ produced some effects that could be related to a high abuse potential. The present investigation was designed to study the specific abuse liability of FNZ in MMP. Eight volunteering MMP (40-50 mg daily) received in a randomized, double-blind, cross-over design the following six single-dose drug conditions: FNZ (1, 2 and 4 mg), triazolam (TZ, 0.5 and 0.75 mg), and placebo. Repeated assessments of subjective effects and psychomotor performance were done over 6 h with a set of 14 visual analog scales (VAS), ARCI 49-item short form, simple reaction time (RT), digit symbol substitution task (DSST), balance, and Maddox wing. No differences were found between placebo and FNZ 1 mg. Active treatments presented a dose-effect relationship in almost all the variables. Both BZD produced increases in sedative-related actions (*e.g.* psychomotor performance impairment). FNZ 4 mg increased ARCI-MBG and high scores in comparison to all other conditions. The results suggest that FNZ could present a higher abuse liability than TZ in MMP.

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COMPARING BEHAVIORAL CHARACTERISTICS OF ALCOHOLICS NEEDING/NOT NEEDING LIVER TRANSPLANT

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Alcoholics are the most common group of individuals presenting for and receiving liver transplants in this country. Considerable debate exists in the literature as to whether alcoholics should receive equitable consideration with other candidates, given the limited supply of available livers and the enormous cost of transplant surgery. Scant data exists comparing alcoholics awaiting liver transplant to alcoholics not in need of transplant, and available information suffers from a lack of rigorous methodology. The purpose of this pilot study is to compare whether drinking patterns, mood states, and motivation for treatment differ in these two populations. This study will compare baseline data from 40 outpatients awaiting transplant who are part of a larger study evaluating the effects of naltrexone/placebo treatment for alcoholism post transplant to 40 outpatients who present for another naltrexone/placebo alcoholism treatment study, but are not in need of transplant. All patients satisfy DSM IV criteria for alcohol dependence. Patients will receive an alcohol breathalyzer, urine drug screen, Serum Carbohydrate Deficient Transferrin, Addiction Severity Index, Treatment Services Review, Time Line Follow Back, Lifetime Drinking History (LDH), Alcohol Craving Scale, Symptom Check List-90, SF-36 (health functioning and quality of life), and the Stages of Change and Treatment Eagerness Scale. Subject recruitment is ongoing; Preliminary results from 8 pre-transplant and nine naltrexone subjects showed no significant differences in sociodemographics, SCL-90, or LDH data. The SF-36 and ASI showed worse health functioning for the pre-transplant group. Clinical observations show a trend for more IV drug use and Hepatitis C in the pre-transplant group. Implications suggest alcohol treatment interventions need not differ for pre-transplant alcoholics. The link with Hepatitis C and other data need further study. ACKNOWLEDGEMENT: Sponsored by NIAAA grant AA00197-02

USING FUZZY LOGIC MODELLING TO PREDICT RESPONSE TO PHARMACOTHERAPY IN ALCOHOL DEPENDENCE

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The serotonin reuptake inhibitor citalopram (C) reduced short-term alcohol intake [AI] in 3 placebo [P]-controlled studies in 162 patients [pts] drinking 6.5±2.7 (x±SD) drks/day. Average decrease in AI was greater with C40 mg/d and brief psychosocial intervention [C+BPI] (47%) than with P+BPI (24%) or C40 mg/d alone (28%); effects of P (6%) and C20 mg/d (0.1%) were lowest ($p<.05$) but SDs>20% indicated wide and unpredictable variations in response. We used fuzzy logic, an alternative to binary logic developed by engineers to deal with the "greyness" of the real world, to attempt to predict responders to C. "If-then" rules were developed to relate baseline AI, age, anxiety, depression, alcohol dependence, alcohol-related problems, and treatment response (% decrease in AI). It showed that older pts (31-66 yrs) responded better than younger (19-58 yrs) and that P and C20 had small effects, but otherwise did not detect differences among treatments. As C40 treatments had the highest average responses and may have clinical use, they were further analyzed. Baseline AI, age, anxiety, depression, and alcohol dependence predicted response to C40+BPI (n=28) with bias of -1.0 and precision of 3.69. Pts who reduced AI >75% drank $\leq$ 6 drks/d in baseline, were 44-63 yrs old and had low anxiety and depression; higher anxiety, depression, alcohol dependence and baseline AI reduced the effect size. Many younger pts (31-52 yrs) had little change in AI, and anxiety reduced response. Another set of rules predicted response to C40 (n=34) with bias of .19 and precision of 3.28. Pts who reduced AI >50% were 26-47 yrs old, drank 5-10 drks/d in baseline, and had low anxiety and depression. Attributes of pts who reduced AI $\leq$ 10% overlapped these ranges, so could not be distinguished from good responders. Thus, fuzzy logic predicted response better than standard statistical methods. Further modelling of response to pharmacotherapy with fuzzy logic is warranted.

ADULT ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN COCAINE ABUSERS: PSYCHIATRIC COMORBIDITY AND PATTERN OF DRUG USE

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This study assessed the prevalence of adult attention-deficit hyperactivity disorder (ADHD) in cocaine abusers seeking treatment. The interview consisted of multiple assessments including: the SCID for DSM-IV (for Axis I and Axis II psychiatric diagnoses), a SCID-like module for adult ADHD, and dual-diagnosis and pattern of drug use questionnaires. At present 204 psychiatric interviews out of 300 have been completed. Twenty four percent had childhood ADHD or childhood ADHD.NOS (not otherwise specified). Of these, approximately 75% continued to have impairing ADHD symptoms into adulthood. An additional 12% of the sample had substance-induced (S-I) ADHD. Individuals with persistent adult ADHD symptoms were more likely to have hyperactive-impulsive symptoms (X^2=7.64, 1 df, $p<0.05$), whereas those with S-I ADHD were more likely to have inattentive symptoms (X^2=5.15, 1 df, $p<0.05$). Affective disorders were the most prevalent additional diagnosis among all groups. Whereas adults with persistent ADHD symptoms most commonly had antisocial personality disorder (30%) those with S-I ADHD most commonly had paranoid disorder (17%). Adults with persistent ADHD achieved the longest period of abstinence: adults with S-I ADHD symptoms spent more money on cocaine prior to seeking treatment. Among individuals with persistent adult ADHD, 67% of those with cocaine abuse/dependence felt that cocaine made their symptoms worse, whereas 60% of those with marijuana abuse/dependence felt that marijuana had no effect or made their ADHD symptoms "better." No one with S-I ADHD felt that cocaine, marijuana, or alcohol improved their ADHD symptoms. Based on these findings, there is a subpopulation of cocaine abusers with adult ADHD symptoms. Although cocaine may initially provide symptomatic relief for some individuals, with continued cocaine use and dependence, cocaine was more likely to exacerbate their psychiatric condition.

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PERSONALITY DISORDER AND DIMENSION DIFFERENCES IN TYPE A AND TYPE B SUBSTANCE ABUSERS

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Previous research has found at least two subtypes of substance abusers which differ on multiple characteristics, including family history, personality, childhood behavior problems, age of onset, symptom severity, consequences, and outcome. Type A seems to be a less severe subtype with fewer premorbid risk factors. The more severe Type B has a higher incidence of Antisocial Personality, but subtype differences have not been examined for the other personality disorders or the normal personality dimensions believed to underlie the personality disorders. The Type A-Type B distinction was replicated and subtype differences in DSM-IV personality disorders and personality dimensions from five (NEO) and seven (TCI) factor models were evaluated in 370 inpatient and outpatient alcohol, cocaine, and opiate abusers. In comparison to Type As, Type Bs were more commonly diagnosed with and had more severe symptoms of all personality disorders except Schizoid. With regard to normal personality dimensions, Type Bs scored higher on Neuroticism, Novelty Seeking, Harm Avoidance, and Cooperativeness, and lower on Agreeableness, Conscientiousness, and Self-Directedness than Type A substance abusers. These subtype differences remained significant after controlling for the effects of antisocial personality and psychiatric symptoms.

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THE ROLE OF AXIS I DIAGNOSIS IN SUBSTANCE ABUSE TREATMENT OUTCOME WITH HOMELESS COCAINE ABUSERS

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This study examined the relation between the presence of DSM-III-R Axis I psychiatric disorders and cocaine addiction treatment outcome in homeless clients. Dually diagnosed clients were hypothesized to be less successful initiating abstinence than cocaine abusers without comorbid psychiatric disorders. Fifty subjects engaged in a larger study of day treatment for cocaine abuse were randomly assigned to either a day treatment only group (Control) or the same day treatment plus abstinent contingent housing and work therapy (Experimental). Psychiatric diagnosis was determined after professional administration of computer guided DSM-III-R interview. Sixty percent of clients had one or more Axis I diagnoses including anxiety disorders (66%), mood disorders (63%), organic mental disorders and syndromes (7%) and other (13 %). A preliminary 2 x 2 Kruskill-Wallis test of urinalysis results obtained over the 8 week treatment revealed control clients with Axis I diagnoses (CA) attained 2 fewer consecutive weeks abstinent than control clients without Axis I (CNOA) diagnoses or experimental clients of ether diagnostic status (EA, ENOA). While clinically important, results were statistically nonsignificant ($p<0.075$), perhaps due to small N. However, when comparing the CA group with the combined EA, ENOA, and CNOA groups, a Mann-Witney U two group test showed a significant difference in consecutive weeks abstinent ($p=.01$). Thus abstinence in the day treatment plus housing and work therapy group did not differ as a function of psychopathology, while it did in the day treatment only group. These results suggest that homeless dually diagnosed clients may have differential treatment needs. Supported by NIDA grant RO1 DA8475

Consecutive weeks abstinent by treatment group and diagnostic status.

Groups	Control	Experimental
Axis I	M=3.0 (SD)=2.8	M=5.0 (SD)=2.7
Without axis I	M=5.2 (SD)=2.4	M=5.3 (SD)=2.6

GENDER DIFFERENCES IN PSYCHIATRIC COMORBIDITY AMONG COCAINE USERS

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High levels of psychiatric comorbidity have been documented previously among substance abusers. The study's purpose was to determine whether distinct clusters of psychiatric diagnoses could be identified, and whether these differed for males (M) and females (F). Subjects: 212 methadone patients all with current cocaine dependence or abuse. Axis I (all) and Axis II (Anti-social Personality Disorder only) diagnoses were made using the Structured Clinical Interview for DSM-III-R-(SCID). Sample characteristics: M (59%) F (41%);1 Hispanic (53%), black (34%) white/other (13%); less than h.s. grad. (59%), h.s./GED (29%) post h.s. (12%). ***Current*** diagnoses were (M/F, in %); mood disorders (38/46), anxiety disorders (24/46, $p<.001$), alcohol (27/21), opioids-illicit (26/24) sedative/cannabis (18/15), ASPD-full criteria (32/17, $p<.05$), ASPD-adult criteria (46/43). In log linear analysis, mood and anxiety disorders were positively associated for F but not for M ($p<.05$) test for interaction); anxiety disorders and adult ASPD were positively associated for F and negatively associated for M ($p<.01$, test for interaction). Certain other diagnostic clusters existed across gender, in particular, continuing dependence on illicit opiates while in methadone treatment was associated with increased risks of sedative/cannabis dependence and mood disorders. Male and female substance users in this population display significant variation in psychiatric comorbidity profiles that may require different clinical interventions. The empirical syndromes identified by multivariate analysis may also have prognostic utility; this should be investigated by further research.

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QUANTITATIVE EEG, COMORBIDITY AND TREATMENT OUTCOME IN COCAINE DEPENDENCE

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This study investigates the retlationship between quantitative EEG (QEEG), comorbidity, and treatment outcome in a population of cocaine dependent adults. Fifty-one males and 27 females with DSM III-R, cocaine dependence, residing in a drug-free therapeutic community, were evaluated 5-14 days after last cocaine use. We have previously reported the existence of a distinctive persistent QEEG profile in such a population, characteritzed by deficits of slow frequencies, excesses of alpha activity, greater anterior abnormalities and inter-hemispheric disturbances. The presence of depression, sociopathy, and anxiety features were assessed by psychiatric and self-rating scales. Existence of comorbid depression and/or alcohol abuse meeting DSM III-R diagnostic criteria was assessed by psychiatric screening. No significant differences were seen in clinical features at baseline between males and females. However, an interaction between gender, comorbid symptomatology, QEEG and length of stay in treatment (LOST) was observed, with females who stay in treatment longer (≥10 weeks) having the lower depressive ratings at baseline, and showing less slow wave deficit and more normal alpha activity in their QEEGs.

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PSYCHIATRIC COMORBIDITY OF COCAINE-DEPENDENT OUTPATIENTS; CORRELATION WITH TREATMENT OUTCOME

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We studied the prevalence of psychiatric comorbidity and its influence on treatment outcome (length of stay [LOS], percent of urine samples positive for benzoylecgonine [%+urines]) in 113 subjects (mean age 33 years [range 21-47 years], 72% male, 68% African-American, 31% white) entering either of two eight-week outpatient medication trials for treatment of cocaine dependence. All subjects received weekly drug abuse counseling and gave urine samples under direct staff observation. Subjects were excluded if they had current severe psychiatric symptoms or need for treatment, based on clinical interview or SCL-90R general distress score >70. DSM-III R diagnoses (Axis I, antisocial personality disorder [ASP]) were generated from the Diagnostic Interview Schedule done during screening. Forty-eightseven percent of subjects had >1 other current (one year) diagnosis, 63% had >1 other lifetime diagnoses. The commonest comorbidities were anxiety disorders (32% of subjects), affective disorders (12%), and ASP (S27%). There were not significant correlations between number of lifetime or current diagnoses or psychiatric symptoms and either outcome variable, except between number of lifetime diagnoses and LOS ($r + 0.21$, $p = 0.03$). Subjects with an affective or anxiety disorder or ASP did not differ significantly from those without one either outcome variable. Women and African-Americans had significantly poorer treatment outcome, possibly confounding the influence of psychiatric comorbidity. These findings suggest that lifetime or inactive psychiatric comorbidity may not influence drug abuse treatment in the same way as current or active comorbidity, which has been associated with poorer treatment outcome.

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PRE- OR POSTNATAL EXPOSURE TO A K AGONIST ALTERS DOPAMINE RECEPTOR DEVELOPMENT IN RAT BRAIN

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To determine if prenatal or posnatal exposure to a k opioid alters brain DA or k receptor development, 14-day osmotic pumps containing U-50488 (U50), 79 mg/ml, or vehicle were implanted into pregnant rats on GD14. At birth, the litters were culled to nine pups per litter with at least four male pups per litter. Pre- and postnatal exposure groups were obtained by cross-fostering litters born to control and experimental mothers. Control litters were cross-fostered to other control mothers. On PD 14 or 28, the brains of male offspring were dissected for nucleus accumbens (Nac) and striatum to determine the binding capacity (Bmax) and apparent dissociatinon constant (Kd) of DA D1, D2, and k opioid receptors. Similar tissues from all male offspring in a given litter were pooled so that each litter represented an n of one with an n of 4-6 litters per group. Prenatal or postnatal exposure to U50 signigicantly ($p<0.05$, ANOVA) increased the Bmax of DA D1, but not D2 or K, receptors in the Nac and striatum of 14- and 28-day-old offspring. Exposure to U50 had no significant effect on the Kd of D1, D2, or k receptors in either brain area at either age. The results suggest that k opioid mechanisms might be involved in the neurological changes observed in offspring born to mothers addicted to opioids during pregnancy.

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DUAL DIAGNOSIS RELAPSE PREVENTION (DDRP): A PRELIMINARY OUTCOME REPORT

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The preliminary findings of our Phase 01, NIDA funded Dual Diagnosis Relapse Prevention (DDRP) psychotherapy development grant are presented. DDRP was developed for schizophrenic substance abuse patients seeking treatment in a community mental health center. In brief, DDRP is a motivation based model which integrates and modifies traditional substance abuse relapse prevention treatment with psychiatric social skills training. It is based on cognitive-behavioral theory and the goals of treatment are linked with a patient's motivational level to change substance use. Our pilot research studies (N=100) suggest that (1) DDRP significantly increased patient treatment attendance (51%) compared with traditional OPD dual diagnosis group (26%); (2) 3 pilot studies of DDRP revealed high rates of treatment completion: 76%, 55%, and 88% and an average reduction in self report cocaine use (46%); (3)Urine toxicology showed reduced rates (46%) and (54%) of cocaine use for two groups of DDRP patients; and (4) Motivation as reflected in stage of change was shown to shift over the course of treatment and appears to be related to a decrease in substance use and an increase in treatment completion and group attendance. These findings support the continuation of DDRP psychotherapy development and completion of a phase 02 randomization study of this promising approach for dual diagnosis treatment.

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EFFECT OF PERINATAL METHADONE (M) ON STRIATAL CHOLINERGIC AND DOPAMINERGIC NEURONS

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The present study was designed to determine the effect of perinatal methadone exposure on cholinergic and dopaminergic neurons. On day 7 of pregnancy, female Sprague-Dawley rats anesthetized with methoxyflurane were implanted s.c. with osmotic minipumps filled with M (9 mg/kg/day) or sterile water (W). Within 24 h of birth, litters were culled to 10, with equal numbers of male and females wherever possible, and fostered to dams implanted with minipumps containing M or W, so that W/W, W/M, M/W, and M/M prenatal/postnatal exposure groups were obtained. On postnatal days 4 and 21 (P4 and P21), striatal acetylcholine (ACh), dopamine (DA), and dihydroxyphenylacetic acid (DOPAC) contents were determined. ACh turnover rate was assessed on P21. A significant prenatal treatment effect was observed on P4 with striatal ACh content significantly reduced in pups from both methadone prenatal exposure groups ($F1,78 = 20.662$, $p < 0.0001$). There was a statistically significant effect of postnatal treatment ($F_{1,30} = 6.296$, $p < 0.05$) as well as a significant interaction between the prenatal and postnatal treatments ($F_{1,30} = 4.241$, $p < 0.05$) on the ratio DOPAC/DA. Consistent with withdawal, this ratio was significantly reduced in M/W rats. On P21 there was a significant prenatal treatment effect on striatal ACh turnover ($F_{1,56} = 11.165$, $p < 0.005$). DA metabolism was not affected in these rats. These data suggest that prenatal exposure, not neonatal withdrawal, disrupts the development of striatal cholinergic neurons.

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METHADONE MAINTENANCE OF ≥ 80 MG DURING PREGNANCY

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Although the use and effects of methadone maintenance during pregnancy have been well investigated, the optimal dose of methadone for maintenance during pregnancy remains a topic of clinical debate. Recommendations vary from low dose, *i.e.,* should be reduced to<20 mg late in pregnancy, to that of lowest "effective dose" which may be in any range and require dose increases even during the last trimester. However, little information exists regarding high dose, <80 mg, during pregnancy. This study presents data for 17 women who received methadone maintenance of ≥ 80 mg during pregnancy ($\bar{x}$=81 mg with a range of 65-106 mg) and 22 women who received <80 mg ($\bar{x}$=52 mg with a range of 31-74 mg). No significant differences were found between groups on birth outcomes [birthweight (<80 mg) $\bar{x}$=2637 gm, (≥80 mg) $\bar{x}$=2674 gm; length (<80 mg) $\bar{x}$=47 cm, (≥80 mg) $\bar{x}$=47 cm; head circumference (<80 mg) $\bar{x}$=31.9 cm, (≥80 mg) $\bar{x}$-32.6 cm; GA (<80 mg) $\bar{x}$ =37 wks, (≥80 mg) $\bar{x}$=37 wks] or severity of withdrawal. Overall, women who received ≥ 80 mg were more successful in reducing their drug use during pregnancy as indicated by percentage of urine drug screens that were positive only for methadone. However, length of time in methadone maintenance treatment, history of other drug use, and maintenance dose prior to pregnancy are factors that must also be taken into account in evaluating methadone dose during pregnancy.

TREATMENT OUTCOME FOR PERINATAL SUBSTANCE ABUSERS HIGH AND LOW IN PSYCHOPATHOLOGY

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Do women high in psychopathology, hypothetically "matched" to treatment, have differential outcomes from low psychopathology women? Outcome for two clusters of perinatal substance abusers in high intensity outpatient treatment was examined. Forty-six women were classified as High or Low psychopathology by MMPI-2 cluster analysis. Mixed models repeated measures ANOVA and univariate t-tests revealed that High and Low groups showed differential improvement on the Addiction Severity Index (ASI), Millon Clinical Multiaxial Inventory-II (MCMI-II), and MMPI-2. The High group improved on ASI Alcohol, Family, and Psychiatric Severity Scores, while the Low group improved only on the Drug Score. Both High and Low groups improved on the MCMI-II's Debasement and Dysthymia scales: the High group on on the Major Depression scale and the Low group decreased on the Borderline scale. Both groups decreased on MMPI-2 scales 2, 3, 4, 6, and 8, reflecting decreases in depression, repression, acting-out, suspiciousness, hostility, and alienation. The High group also decreased on scale 7 (anxiety, rumination) and the Low group decreased on scale 1 (somatization). High intensity, perinatal-specilic treatment produced significant change in both high and low psychopathology subjects. High psychopathology subjects experienced symptomatic relief and lowered psychiatric severity, while Low psychopathology subjects experienced improvement in acting-out, somatic complaints, and general distress. Greater numbers of scales improved for the High group, possibly indicating more improvement due to "matching" of subjects to treatment intensity. Future research should investigate whether Low psychopathology women, 75% of the perinatal substance abuse sample, would benefit equally well from less intensive treatment. ACKNOWLEDGEMENT: Supported by NIDA grant DA-06094

CHANGES IN METABOLISM OF METHADONE DURING PREGNANCY

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Previous studies have shown that the half-life of methadone is reduced during the late stages of pregnancy. Further studies are in progress to explain the changes in metabolism. Both pregnant and non-pregnant methadone-maintained subjects were admitted under an IRB-approved protocol to the Clinical Research Center at the Medical College of Virginia. Plasma methadone levels were collected at defined intervals throughout one 24-hour period, with subjects at steady state on an oral regimen. The following parameters were calculated using the iv methadone levels from two patients: The concentration vs. time plots permitted calculation of the area under the curve (AUC) which was used to calculate total body clearance rates for both groups. Total body clearance is comparable to previously published data[1], though renal clearance is substantially decreased. Volume of distribution is greatly expanded, as would be expected during pregnancy. The half-life of methadone was found to be significantly decreased during pregnancy as compared to the non-pregnant state. Median pregnant half-life of 20.4 was compared to the median non-pregnant half-life (32 hours) using the Wilcoxin Rank sums test, and was found to be significant ($p = .0503$). These studies will help to define the alterations in methadone metabolism that occur in pregnancy and assist in developing better dosing procedures for pregnant women.

[1]Inturrisi, *et al.* 1987. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. *Clinical Pharmacology and Therapeutics.* **41**:293-401.

PRENATAL COCAINE EXPOSURE AND PERCEPTUAL DEVELOPMENT: EFFECTS AT FOUR AND SEVEN MONTHS

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Infants' sensitivity to implied orientation contours inherent to herringbone patterns in healthy non cocaine-exposed (Non-CE) and cocaine-exposed (CE) infants was assessed using a visual recognition memory (VRM) paradigm. Adults perceive a global orientation from the arrangement of local line segments oriented at right angles to each other, independent of orientation. Global perception of these patterns before 3 mo is highly orientation-specific, with normal infants demonstrating emerging sensitivity only along the cardinal axes (horizontal and vertical) and not along the obliques. Present results indicated a significant CE by Familiarization Orientation interaction at both 4- and 7-mo, which can be attributed to a differential novelty response between Non-CE and CE infants. Non-CE infants, as expected, demonstrated novelty responses along the cardinal axes, whereas CE infants demonstrated novelty responses along the oblique axes. As the detail of the local elements within the oblique herringbones are oriented along the cardinal axes, novelty responses of CE infants may not be based on general global aspects of the pattern. These data suggest a continuation of CE infants' stimulation-seeking behavior and atypical perceptual organization that may underlie a divergent developmental trajectory.

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RESPIRATORY FUNCTION IN JUVENILE RHESUS MONKEYS EXPOSED PRENATALLY TO COCAINE

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Clinical epidemiological and case studies have reported that prenatal exposure to cocaine may result in altered respiratory function and increased risk of Sudden Infant Death Syndrome (SIDS). This study characterized respiratory function in juvenile rhesus monkeys, ages 3-4 years, after prenatal exposure to cocaine (0.3 mg/kg/hr) from day 24 post-conception throughout gestation. Ventilation was measured continuously in conscious monkeys with a head plethysmograph during exposure to air (normocapnia), 3%, 4% and 5% CO_2 balanced in air (hypercapnia), 10% O_2 balanced in N_2 (hypoxia) and 100% O_2 (hyperoxia). Cocaine (0.03-3.0 mg/kg) was administered acutely to assess potential changes in sensitivity to its physiological effects resulting from prenatal exposure. Caffeine (1.0-30.0 mg/kg), an efficacious respiratory stimulant, also was administered acutely to assess further the neural control of respiration. Cocaine-exposed (N=4) and pair-fed controls (N=4) exhibited typical respiratory function characteristic of normal adult rhesus monkeys, and there was no significant difference among treatment groups in sensitivity to the respiratory-stimulant effects of cocaine or caffeine. The results demonstrate normal respiratory function in juvenile rhesus monkeys exposed prenatally to cocaine.

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ASSESSMENT OF NURSES' ATTITUDES TOWARD PREGNANT SUBSTANCE ABUSING WOMEN FOLLOWING INSERVICES

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Background: The attitudes of labor and delivery (L & D) RNs caring for substance-abusing pregnant women may affect care due to biases, which in turn influence compliance and other factors associated with OB care. Introduction of a mandatory staffing inservice may influence attitudes and opinions of RNs providing care to this population. **Purpose:** To describe the attitudes of RNs in a metropolitan, tertiary care hospital L & D unit providing prenatal care to substance-abusing women before and after inservice. **Methods:** 30 surveys were distributed to a random sample of RNs in an L & D unit 1 month prior to, immediately following, and two weeks after an inservice to increase awareness of prenatal care strategies for substance abusing women. **Results:** (N=22) (a) Experience: Over 50% reported caring for women using marijuana, cocaine and methadone. Less than 20% reported caring for women using cigarettes and alcohol. (b) Teratogenic Effects on Fetus: Heroin, cocaine and benzodiazepines were reported as most harmful, whereas cigarettes and alcohol were reported to be least harmful. (c) Delivery Interventions: Referral to OB social worker was most frequent intervention of choice for substance abusing pregnant women. (d) Urine Drug Screens: The majority reported ordering UAs on all women presenting to L & D with complications. (e) Drug-positive UAs: Prior to and immediately following the training, 30 to 45% of nurses reported that a positive UA was the best reason to call Child Protective Services (CPS) or the OB social worker. Two weeks later, no RNs reported this ($p=0.012$). Prior to training, 90% of RNs reported that all positive UAs should be reported to CPS. Immediately after, there was a significant decrease in nurses who felt this ($p=0.013$), but a return to baseline two weeks later. **Conclusions:** (1) Lack of knowledge of the harmful effects of cigarettes and alcohol on the fetus is a concern. (2) Training had some impact in the areas of the significance of positive UAs, however, some changes were short-lived.
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INTERVENTION WITH CHEMICALLY-DEPENDENT PREGNANT WOMEN: PSYCHOSOCIAL, PARENTING, & INFANT OUTCOME

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A multicultural sample of 208 polydrug-using pregnant women were assessed upon randomized entrance into one of three groups: short-term residential or intensive outpatient comprehensive services (both hypothesized to yield positive mother and infant outcomes), or standard community treatment. At baseline, study participants were seriously chemically-dependent and showed high levels of psychological distress. Pre-post comparisons of follow-up participants showed most women had improved significantly over the first year from baseline, regardless of treatment modality. For example, self-reported depression and stressful life events had decreased (e.g., Beck Depression Inventory baseline $\underline{M}=19.76$; follow-up $\underline{M}=11.21$). On average, parenting behaviors were adequate for birth mothers retaining child custody at follow-up (e.g., HOME Total $\underline{M}=34.79$). At 4 to 5 months of age, infants followed were within normal limits on standard developmental measures (e.g., Bayley MDI $\underline{M}=107.29$), regardless of treatment modality. However, there were indications of risk: 44% of these infants scored above a clinical cutoff for neuromotor risk on the MAI-ST, and at follow-up 24% of women scored below the 10th percentile on the NCAST Teaching Scale. Analyses are ongoing to identify predictors of poor outcome, such as developmental decline in a subset of infants followed through age one year. As in many studies of this population, there was considerable sample attrition due to caregiver noncompliance. Findings suggest cautious optimism about intervention, and underscore the need to retain chemically-dependent pregnant women in treatment.

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CHILDREN AT RISK: PRELIMINARY FINDINGS

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This paper reports on preliminary findings of a five-site, three year national research and demonstration program that concluded in 1995 and is now being replicated in additional cities. The program brings together local networks of city agencies, non-profit service providers, schools, police departments, and juvenile justice agencies to serve high risk 11-13 year olds and their families living in impoverished urban neighborhoods. It is designed to prevent delinquency and drug use among youth and to reduce drug related crime in the neighborhoods where they live. Preliminary findings are based on official records of the first 228 youth recruited in the program. Analysis of officially recorded police and juvenile court contacts shows the CAR participants had 41 contacts with the police compared to 69 contacts for the randomly assigned control group. xamining school performance, 88% of CAR students compared to 72% of control students were promoted in the 1992-93 school year; in the following year, 82% of CAR youth compared to 70% of the controls were promoted. All of these findings were statistically significant.

DIAGNOSING DRUG DEPENDENCE IN PREGNANT WOMEN: FAMILY INFLUENCE ON DRUG SEVERITY

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Diagnosing drug dependence is an important component in the treatment of substance use disorders. Epidemiological studies have found increased drug use in females of child-bearing age as well as pregnant women. Family influence of substance use has historically been an important correlate in the treatment of substance abusers. By identifying and understanding this familiar link, effective and appropriate treatment can be designed to target the specific needs of such special populations. A sample of 175 pregnant women who presented for treatment at the Center for Addiction and Pregnancy in Baltimore, MD., were administered the Family Alcohol and Drug Survey (FADS) and the Structured Clinical Interview for DSM III-R (SCID). The purpose of this study was to examine the relationship between: 1) family history of drug/alcohol abuse and patient drug abuse severity; 2) patient age of onset of substance use and patient drug abuse severity; and 3) family history of drug/alcohol abuse and patient age of onset of substance use. Drug abuse severity was calculated from the SCID using the total number (range 3-27) of Alcohol, Opioid, and Cocaine dependence criteria with a threshold diagnosis score. Results indicated that patients with a positive family history of heavy problematic alcohol abuse evidenced greater drug severity scores than patients with a negative family history of alcohol abuse. In contrast, there was no significant difference in drug severity scores between subjects with a positive history of drug abuse and those with a negative family history of abuse. This result was consistent for both maternal and paternal substance abuse. Also, while an ealier age of onset suggested increased drug severity scores on the SCID, these significant results did not appear to be the result of parental substance use, suggesting that these two effects are independent. While a family history of alcohol abuse and earlier age of onset of substance use appear to influence drug severity, further study into this area is warranted.

SPONTANEOUS MOTILITY: A BIOLOGIC MARKER OF SUBSTANCE RISK IN ADOLESCENTS?

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Conduct disorder (CD) often co-occurs with substance use disorder (SUD). CD may be worsened by comorbid attention-deficit hyperactivity disorder (ADHD). Does ADHD also worsen the SUD of youths with CD? HYPOTHESES: Among youths with CD, those with greater spontaneous motility will have (A) more substance involvement, (B) more severe ADHD, and (C) more severe CD. METHODS: In a treatment program we assessed spontaneous motility of 62 males (ages 13-18) with carefully assessed CD and SUD. They had been abstinent at least 5-28 days. Actometers recorded body movements continuously for 20-48 hrs. A teacher rated classroom activity (Conners scale; n = 57). RESULTS: (A) Motility correlated significantly with number of drugs used regularly (partial r = .38; p = .0005), but not with certain other measures of substance dependence. In a multiple regression (adjusting for actometer differences) motility (p = .0001), CD symptom count (p < .06), and CD onset age (p < .08) predicted number of drugs used regularly (multiple R = .54; p = .0004). (B) Motility correlated significantly with Conners ratings (partial r = .39; p < .003) but not significantly with ADHD symptoms. (C) Motility did not correlate significantly with lifetime number of CD symptoms. CONCLUSION: Among abstinent adolescents with CD and SUD motility levels assess aspects of ADHD and are strongly associated with number of drugs used.

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ACADEMIC FUNCTIONING IN CONDUCT-DISORDERED ADOLESCENT SUBSTANCE ABUSERS

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We assessed the academic skills of 207 delinquent adolescent males, ages 13-19, in treatment for conduct disorder/substance problems and hypothesized that academic delay would be related negatively to intelligence (IQ) and positively to substance dependence symptoms (SDS) and psychiatric symptoms (PSY). Scores on the age-appropriate Wechsler intelligence scale and the Woodcock-Johnson Tests of Achievement-Revised were used. We computed academic delay scores by subtracting the obtained grade score from the last grade completed for four domains (Broad Knowledge, Reading, Math, Written Knowledge) and then calculated the mean (AvDelay). AvDelay was 0.94 (almost one year) and mean Wechsler Full Scale IQ (FSIQ) was 96. Strong correlations occurred between AvDelay and FSIQ (r = -.57, p<.01). Total SDS also correlated negatively with AvDelay (r = .21, p<.01) and with FSIQ (r=.24, p<.01). No significant correlations were found between PSY and AvDelay. As predicted, Academic delay and IQ were negatively related. Contrary to expectations, AvDelay and SDS were also negatively related, so that less academic delay was associated with more substance dependence symptoms. Possible explanations will be presented.

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PREVALENCE OF SUBSTANCE USE DISORDERS AND PSYCHIATRIC COMORBIDITY AMONG GEORGIA JUVENILE OFFENDERS

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This study was conducted to estimate the prevalence of DSM-III-R substance use diagnoses and psychiatric comorbidity among the juvenile offender population entering the 20 Regional Youth Detention Centers operated by the Georgia Department of Children and Youth Services. A stratified random sample was selected, using facility and gender as stratification variables, with oversampling of females. The sample consisted of 178 white males, 287 African American (AA) males, 93 white females and 121 AA females plus 16 males and 6 males of other ethnic groups, for a total sample size of 701. Interviews consisted of the SCL-90-R, the Childhood Trauma Questionnaire (CTQ) and the DISC-C v2.3 and were administered within 72 hours of admission. Weighted estimates reflecting the sample design were obtain using PC-SUDAAN. The prevalence of substance use disorders was 30.1 ± 4.3%, ranging from 42.9 ± 9.1% in white males to 11.7 ± 6.3% in AA females. The prevalence of marijuana dependence was highest in all groups at 22.4 ± 4.1% overall, followed by alcohol dependence at 14.4 ± 3.5% and other drug dependence at 7.2 ± 2.4%. Dependence on drugs other than alcohol and marijuana was much more prevalent among white subjects. Comorbidity, the prevalence of other psychiatric disorders in subjects with substance use disorders, was very high: 37± 8% for anxiety disorders, 29 ± 8% for affective disorders and 62 ± 8% for disruptive behavior disorders. Scores on the CTQ, which is a self-report of child abuse, were not associated with SU disorders. No measure so far examined in the study is statistically associated with the ethnic differences in the prevalence of SU disorders. ACKNOWLEGEMENT: Supported by CSAT 270-94-0010 and the GA Policy Design Academy.

SUBSTANCE ABUSE AND PSYCHIATRIC EFFECTS ON PLATELET AGONIST-INDUCED DENSE GRANDULE SECRETION IN ADOLESCENTS

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We previously reported a reduction in agonist-induced platelet dense granule ATP secretion in abstinent adolescent male substance abusers with conduct disorder. The pattern of diminished agonist responses suggested that an alteration in signal transduction mechanisms rather than surface receptors properties could account for the observation. In order to examine the specificity of both drug use effects and the manifestations of psychiatric disorders on platelet dense granule responses, we significantly expanded the adolescent sample to include those with and without conduct disorder and other psychopathology. Specifically, the effects of conduct disorder, attention deficit hyperactivity disorder, cigarette smoking, an alcohol use disorder, a cannabis use disorder and a cocaine use disorder on platelet dense granule secretion were examined. **Method:** One hundred and ninety-three abstinent adolescents were recruited (145 with Conduct Disorder and Substance Abuse). Fasting platelet-rich plasma was obtained from subjects at 9 AM after an overnight stay at our laboratory. Platelet secretory responses to collagen, thrombin, arachidonic acid, adenosine diphosphate (ADP), ADP + 0.2 ugm 5-HT, and ADP + 1.0 ugm 5-HT were evaluated within 5 hrs. of sampling using an impedance aggregometer. **Results:** All possible subsets regression revealed a significant effect for the presence of an Alcohol Use Disorder on agonist-induced platelet dense granule secretion across several agonists. Specifically, adolescents with an Alcohol Use Disorder (AUD) showed significantly reduced ATP secretory responses to collagen, thrombin, ADP, ADP + 0.2 ugm 5-HT, and ADP + 1.0 ugm 5- HT, but not arachadonic acid. **Discussion:** The results suggest that there may be impairments in platelet signal transduction adolescent boys with an AUD. The platelet signal transduction alterations produced by AUD could also be occurring in parallel at the level of the central nervous system, the endocrine system, and the immune system. Such effects could produce dysregulation of the integrity of each of these systems critical to biological and cognitive maturation.

A STUDY OF THE PREVALENCE OF SUBSTANCE ABUSE AND A VIOLENT BEHAVIOR AMONG AFRICAN AMERICAN YOUTH

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Within the lower socio-economic strata of the African American community, there are a number of substance cases and violent behavior acts committed by children and adolescent populations. One of the leading causes of this concern may be associated with counter productive methods of dealing effectively with what is perceived as anxiety producing stress factors stemming from the environment. Many have debated that stressful social conditions are the major cause of mental disorders in African Americans and thus psychopathology can be prevented. A pilot study was conducted using a sample size of 300 African American youth. Instruments used included a questionnaire developed by the researchers, a self-esteem inventory, a stress index, and depression scale. Results indicated a high correlation between SES, substance abuse and violent behavior. It was concluded that harbored deep within the psychic of this group are feelings of helplessness regarding the harsh reality of racism, oppression, domestic violence, street violence, and the epidemiological influences of AIDS which make for an increase of addictive and malicious behavior.

IMPROVING RESIDENTIAL SUBSTANCE ABUSE TREATMENT FOR INNER-CITY TEENS: NEW HAVEN ACTS

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When compared with other teens needing treatment for substance abuse, inner-city youth typically enter treatment systems later in the abuse-addiction cycle and largely through contact with the criminal justice system. To better meet the needs of inner-city teens, a consortium of agencies developed a comprehensive, culturally sensitive treatment network organized around a neighborhood-based system of case management. One of the primary goals of the initiative was to improve access to services and retention rates for inner-city teens in need of long-term residential treatment. Quantitative evaluation of the initiative demonstrated that systems of care with a single point of entry can be used to clarify the residential treatment needs of specific populations, and evaluation of admission rates using a quasi-experimental research design suggested that the case management component had a significant impact on access to treatment. The results also suggested that staffing enhancements designed to increase cultural competence within the residential component contributed to improvement in retention rates for all clients such that, although improved, retention rates for minority clients remained poorer than those for Caucasian clients. The project illustrates how systems of case management can be used to better characterize the treatment needs of an underserved population and increase access to services. The findings also highlight need for further conceptualization and evaluation of interventions designed to address the special needs of ethnic minority youth with serious substance abuse problems.

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CIMETIDINE MAY DECREASE OPIATE WITHDRAWAL SYMPTOMS IN METHADONE PATIENTS

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Cimetidine, a potent inhibitor of the P450 Cytochrome enzyme system, affects the clinical response of many co-administered medications. To test if administration of cimetidine increases methadone blood levels (or the effective clinical half life) and thus reduces opiate withdrawal symptoms, we estimated the severity of opiate withdrawal symptoms, and obtained blood levels and urine toxicologies for heroin in ten methadone maintained patients, before and during cimetidine treatment for dyspepsia. Nine of ten patients were satisfied with the intervention and said they felt better. Of six patients who rated their opiate withdrawal symptoms on a clinical scale, five reported a reduction of symptoms from a pretreatment average of 6.0 (of a possible 48) to 2.8 after initiation of cimetidine. Methadone blood level was increased by more than 5 ng/ml in six patients, remained the same in two patients, and was reduced in two patients. The overall average methadone level showed a modest increase from 252 ng/ml to 260 ng/ml. For the five weeks prior to treatment, the group gave 40% (18/45) heroin free urines. For the five weeks following initiation of treatment, 53% (24/45) were clean. These observations suggest that co-administration of cimetidine decreases opiate withdrawal symptoms in some methadone maintained patients.

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METHADONE INCREASES ZIDOVUDINE EXPOSURE IN HIV-INFECTED INJECTION DRUG USERS

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Large numbers of injection drug users are HIV-infected and receive both methadone and antiretroviral therapy. To ascertain whether methadone alters zidovudine (AZT) disposition, oral and intravenous AZT pharmacokinetics are being determined in 10 HIV-positive subjects, before and two weeks after initiation of methadone maintenance. Interim analysis (n = 5) revealed that methadone therapy produced an average increase of 52% in the area under the AZT time-concentration curve (AUC) after oral AZT administration ($p = 0.003$, paired t-test). This appeared to result from trends toward an increase in bioavailability (18%; $p = 0.09$) and a decrease in clearance (22%; $p = 0.12$). The intravenous AZT AUC increased an average of 30% ($p = 0.10$), reflecting the decreased clearance. Measurement of urinary AZT and its glucuronide (AZT-G) after oral administration revealed a 42% average increase in excretion of unchanged AZT ($p = 0.12$) with no substantive change in renal AZT clearance or in total urinary recovery of AZT + AZT-G. These findings suggest that methadone reduces AZT glucuronidation, both during first-pass metabolism, thereby increasing bioavailability, and afterwards, decreasing clearance. Both effects increase AZT exposure. The clinical consequences of this interaction require further study. The combination of methadone with AZT may result in increased AZT toxicity and contribute to decreased compliance.

DIFFERENTIAL EFFECTS OF NALMEFENE AND NALOXONE ON HYPOTHALAMIC PITUITARY ADRENAL (HPA) AXIS FUNCTION IN NORMAL CONTROLS

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Opioid antagonists have been proven to be useful as specific probes in elucidating the relationship between the endogenous opioid system and the HPA axis, in performing studies in vitro, in animal models, and in humans. The antagonists which may be used in man are limited in number and are primarily mu opioid selective. However, preliminary studies from our laboratory (Kreek et al., INRC, 1987) suggested that nalmefene (NLM), an opioid antagonist with evidence of substantial kappa as well as mu receptor activity, might have different effects on the human HPA axis than naloxone (NLX), a primarily mu receptor selective antagonist with some kappa activity. With renewed access to NLM, we have now conducted a controlled inpatient study in the NIH-supported GCRC of the Rockefeller University Hospital to compare the HPA effects of 10 and 30 mg. of NLX with those of 30 mg. of NLM (similar molar amount, greater potency in opioid overdose reversal, longer half life), each administered intravenously. Thirteen healthy volunteers with no significant general medical, psychiatric, or substance abuse problems served as their own controls, each receiving a placebo, and at least one antagonist, on separate days. Modest, similar, increases in ACTH and cortisol (F) were seen after either dose of NLX, suggesting that each of these doses yielded close to maximal HPA activation, or a ceiling effect. However, a greater and subsequently more prolonged incrcasc in ACTH and F was observed after 30 mg. of NLM than after either dose of NLX. The results suggest that kappa receptors may have an important role in the regulation of the HPA axis, and that nalmefene may be a useful probe for the study of human neuroendocrine physiology in general, and for the study of the addictive diseases in particular. ACKNOWLEDGMENTS: Supported in part by grants : DA-P50-05130, DA00049, and M01-RR001

THE EFFECT OF FLUCONAZOLE ON THE CLINICAL PHARMACOKINETICS OF METHADONE

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The possibility of a drug--drug interaction between fluconazole (FLU) and methadone was evaluated in 25 methadone-maintained patients. The study was a randomized, double-blinded, placebo-controlled, pharmacokinetic and safety study in which patients received either oral FLU 200 mg/day (n=13) or placebo (n=12) for 14 days with their individual daily methadone dosage. Serum and urine specimens were collected at intervals over a 24-hour period at baseline and after 14 days. There was a 30% increase in serum methadone concentration (AUC) observed in patients receiving FLU (p=0.0008). Consistent with the AUC increase, the oral clearance (Clo) of methadone was significantly reduced by 26% in the FLU group (p=0.0007). The minimal concentration (Cmin), maximal concentration (Cmax), and steady-state concentration (Css) of methadone were all increased by 41% (p=0.0076), 23% (p=0.0023) and 30% (p=0.0008), respectively, in patients receiving FLU. There was no significant difference in methadone renal clearance (Clr) or urine pH after 14 days of FLU therapy. At baseline, mid-study and after 14 days, patients were assessed for signs and symptoms of narcotic withdrawal and overdose. Concomitant administration of FLU and methadone did not precipitate signs or symptoms of narcotic overdose based on the symptomatologic data. On a scale of none (0), mild (+1), moderate (+2) and severe (+3), the few symptoms reported were mild and are not pathognomonic of narcotic withdrawal or overdose. No modifications of methadone dosage were warranted during the study. Although significant changes in methadone pharmacokinetics were observed after concurrent administration of FLU, the combination did not appear to produce any changes of clinical significance in methadone-maintained patients.

DISULFIRAM TREATMENT OF COCAINE ABUSE; FINDINGS FROM A DOSE-RESPONSE STUDY

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Disulfiram (DS), a pharmacotherapy for alcohol abuse which inhibits various enzymes by irreversible binding of sulfhydryl groups and chelation of trace metals, has shown some evidence of efficacy for cocaine dependence in outpatient studies. This dose response study was designed to elucidate the effects of DS on acute cocaine (C) ingestion. Five cocaine-dependent subjects were randomized to DS placebo, 250 mg or 500 mg and pretreated for three days prior to cocaine study sessions (random assignment to intranasal C placebo, 1 or 2 mg/kg). Pharmacokinetic, physiological and behavioral measures were obtained over 480 min. Cocaine (2 mg/kg) AUC was increased four-fold (C: 50828 ng.ml/min vs C/DS 250 mg: 198390 and C/DS 500 mg: 204668) and oral clearance was reduced five-fold (C: .037 L/kg/min vs C/DS 250 mg: .0074 L/kg/min and C/DS 500 mg: .0075L/kg/min). Heart rate increases were prolonged following both DS treatments (C 2 mg/kg: mean increase +13 bpm (peak: 88 bpm); return to baseline by 180 mm.; CIDS: mean increase +16 bpm (peak 91 bpm); remained +9 bpm above baseline at 480 min. "High" was prolonged following C/DS administration. "Bad Effects" were increased following C/DS administration and included nausea/dyspepsia, "palpitations" and chest tightness without ECG changes, depression/tearfulness, anxiety, and restlessness. While there is some potential for cocaine toxicity in patients treated with disulfiram, it may be an effective treatment for selected patients. This study also underscores the importance of determination of plasma cocaine concentrations to evaluate for potential drug interactions in novel drug combinations.

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FORMATION AND ELIMINATION OF COCAETHYLENE IN HUMANS

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Ethanol alters the biotransformation pathways of cocaine, resulting in transesterification to a novel metabolite, cocaethylene (benzoylecgonine ethyl ester). Cocaethylene and possibly other cocaine metabolites are pharmacologically active and may mediate toxic reactions to cocaine. To assess the pharmacology of this interaction, in a balanced, double-blind, placebo-controlled experiment, 10 subjects received, on three separate occasions, doses of deuterium-labeled cocaine (penta-deuterated on the benzoyl moiety), 0.3, 0.6, and 1.2 mg/kg iv over 15 min, combined with cocaethylene (trideuterated on the ethyl moiety), 7.5 mg iv over 15 min, and oral ethanol, 1 g/kg po over 30 min. Use of stable isotope methodology allows for determination (both quantitative and qualitative) of clinically important cocaine metabolic pathways. Plasma and urine levels of d_5-cocaine, d_3- and d_5-cocaetbylene (CE), and d_0— and d_5—benzoylecgonine (BE) and urine levels of d_3— and d_0—ecgonine ethyl ester (EEE) and d_0—ecgonine methyl ester (EME) were determined. Behavioral and cardiovascular effects of the drug combinations were evaluated. With the experiment 75% completed and the blind still in place, data available for interpretation indicate expected metabolic conversion of d_5—cocaine to d_5—CE, d_0—EEE, d_0—EME and d_5—BE. d_3—CE is metabolized to d_3—EEE and d_0—BE. EEE (d_0 and d_3) levels in urine are about tenfold greater than corresponding CE levels. EEE may be a better marker of combined cocaine and ethanol use than cocaethylene alone. Quantitative pharmacokinetics and dynamics, including dose proportionality, will be presented.

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INFLUENCE OF INFUSION RATE AND DOSE ON EFFECTS OF IV COCAINE IN HUMANS

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More rapid delivery rates of cocaine to the blood are believed to increase cocaine's physiological and behavioral effects; however, this has not been studied in humans. In a within-subjects, pseudo-Latin square design, human IV cocaine users received each of 3 cocaine doses (10, 25 or 50 milligrams) at each of 3 infusion durations (10, 30 or 60 seconds, yielding infusion rates of 0.17-5.00 mg/sec) over 10 sessions (1 placebo) on alternate days, administered in a double-blind, double-dummy manner using a 3-way infusion apparatus. Baseline and Post-Infusion Time (2, 4, 7, 10, 15, 21, 26, 31, 36, and 41 minutes) measures of Heart Rate (HR), Systolic (SBP), Diastolic (DBP), and Mean Arterial (MAP) Blood Pressure and subjective effects (Visual Analog Scale, VAS) were analyzed using a 3-way (Dose(3) x Duration(3) x Time(11)) repeated measures ANOVA. Preliminary results (N=3) show significant ($p<.05$) Dose-related increases in HR, SBP, DBP, and MAP. Duration was inversely associated with increase in DBP; no other main or interaction effects were found. On VAS items, significant Dose-related increases in self-ratings of "Rush," "High," "Crave Cocaine," "Stimulated," "Want Cocaine," and "Strong," "Good," and "Like" drug effect were found. Duration was inversely associated with magnitude of peak increase in "High" and "Strong" drug effect, and Dose x Duration x Time interactions were found for "Like" drug effect and "Want Cocaine." These preliminary data suggest that drug delivery rate's influence is more subtle than that of cocaine dose. A broader range of infusion rates may be necessary to show the expected differences. This study's double-blind nature may also be dampening experimenter and subject expectancy effects which have influenced other studies and behavior in the natural environment.
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EFFECTS OF INTRAVENOUS INJECTION SPEED ON RESPONSES TO COCAINE OR HYDROMORPHONE IN HUMANS

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It is widely believed that the speed of intravenous injection is an important determinant of the magnitude of effect of abused drugs. This study examined the effect of intravenous injection speed upon indices of abuse liability and toxicity (i.e., acute subjective and physiological responses) for cocaine and hydromorphone in volunteers who were experienced intravenous abusers of cocaine and opioids. Intravenous challenge injections of cocaine (30 mg), hydromorphone (3 mg) and saline were administered at each of three injection speeds (2, 15 and 60 sec) in a mixed order under double-blind procedures. Standardized subjective effect measures were collected, and heart rate, blood pressure, EKG, skin temperature, pupil diameter and respiration rate were recorded throughout each session. For hydromorphone, neither subjective nor physiological responses were appreciably altered by injection speed. For cocaine, faster injection speeds produced elevations in subjective effects; ratings of "drug effect" and "rush" were significantly elevated following the 2 sec versus the 60 sec injection of cocaine. Importantly, cardiovascular response was not significantly altered by the speed of cocaine injection. These results suggest a considerable margin of safety with respect to variations in the speed of cocaine injection, and suggest a dissociation between the subjective versus cardiovascular effects of cocaine. Experimentally, variation of injection speed might be a useful means for varying the pharmacodynamic effects of cocaine while minimizing total drug exposure and potential cardiovascular risk.

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IMMEDIATE CARDIOVASCULAR EFFECTS OF RAPID IV COCAINE IN EXPERIENCED HUMAN COCAINE USERS

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Some studies in monkeys find that the initial cardiovascular (CV) effect of rapid cocaine administration (IV bolus, smoked) is transient bradycardia, followed by the tachycardia commonly observed in other studies. This effect has been attributed to vagal stimulation or direct suppression of the cardiac pacemaker because of catheter tip placement. Initial bradycardia has not been reported in human studies of IV cocaine administration, but may have been missed because of the timing and methods used to measure heart rate, or the use of only experienced cocaine users as subjects. We are evaluating this question in experienced cocaine users administered IV cocaine double-blind at rates of 0.17-5 mg/sec (total dose 10-50 mg, total infusion duration 10-60 seconds). Heart rate and blood pressure are recorded beat-to-beat using an infrared photoplethysmograph device (Finapres, Ohmeda) worn on the middle finger, and averaged over six seconds to smooth out "noise", Preliminary findings from the first two subjects (26, 30 year old men, nine years of cocaine use) (nine cocaine, one placebo infusion each) show tachycardia beginning within the first minute, with no initial bradycanlia. Findings from this study should elucidate whether experienced human cocaine users show an initial bradycardia with rapid IV cocaine administration.

TOLERANCE TO THE CARDIOVASCULAR AND SUBJECTIVE EFFECTS OF COCAINE DURING BINGE SELF-ADMINISTRATION

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While acute tolerance to the cardiovascular and subjective effects of repeated cocaine doses has been observed within single laboratory sessions, little is known about tolerance to cocaine over longer time spans. Eleven experienced cocaine users, including live maintained on methadone, completed a protocol investigating changes in cardiovascular activity and behavior during multiple self-administration sessions. During sessions, which modeled binge behavior, 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 session occurred in the afternoon and again two hours later in the evening on two consecutive days, while during the 3-cycle condition, sessions occurred on three consecutive days. Plasma cocaine levels, cardiovascular measures and self-reported effects were obtained during each session. Plasma cocaine levels increased with each dose of cocaine. Tolerance to cardiovascular and subjective effects was found to develop within sessions; heart rate and blood pressure increased following the first cocaine dose in each session but did not increase following repeated doses within that session. Ratings of "high," "stimulated," and opiate symptom scores followed the same pattern. "I want cocaine" scores, however, decreased slightly within self-administration sessions. The cardiovascular and subjective effects of cocaine were similar between sessions on the same day and between days. Thus, tolerance to cocaine may be limited to acute tolerance during repeated dosing, with little tolerance observed between binges or consecutive days.

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LESS-THAN-DAILY BUPRENORPHINE DOSING

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Buprenorphine's clinical utility as an opioid dependence pharmacotherapy would be improved if it could be administered on a less-than-daily basis. **Purpose:** To assess the ability of buprenorphine-maintained patients (8 mg/day s.1.) to tolerate 72 hrs of dose omission after receiving buprenorphine doses of 8 and 16 mg. **Methods:** Outpatients (n = 8) maintained on 8 mg buprenorphine and free of illicit drug use completed 4 experimental conditions ordered by Latin-square and given double-blind at weekly intervals, Two test conditions of 8 and 16 mg s.1. buprenorphine were followed by 2 days of placebo. Two control conditions were included: 1) buprenorphine maintenance (8 mg/day) provided a baseline for comparison of withdrawal effect measures on placebo days, 2) a naloxone challenge (10 mg/70 kg) 23.5 hr after an 8 mg maintenance dose of buprenorphine demonstrated sensitivity of withdrawal effect measures. Pupil diameter and subjective measures of opioid withdrawal were collected at pre-test and at 0.5, 1, 2, 3, 25, 49, and 71.5 hr after test dose administration. **Results:** Reliable subjective withdrawal was reported only after naloxone challenge. **Conclusion:** The lack of subjective withdrawal during 71.5 hrs of dose omission suggests that less-than-daily dosing may be clinically feasible at buprenorphine maintenance doses of 8 mg/day or more.

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THE LIMITS OF MULTIPLE-DAY DOSING WITH BUPRENORPHINE; QUINTUPLE DOSES

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This study compares 24-, 72-, and 120 hour buprenorphine (BUP) dosing schedules in opioiddependent outpatients. To date, 12 subjects receiving BUP (sublingual maintenance (M) doses = 4 mg/70 (n =6) and 8 mg/kg (n=6) have completed a double-blind, placebo--controlled, cross-over trial. Prior to condition initiation, subjects were exposed to five times their M dose (20 or 40 mg/70 kg) under laboratory observation, and measures of opioid agonist effects were assessed using the Analog Rating Scale and observer ratings of opioid agonist effects. Observer and subjective ratings of agonist effects were minimal. Following baseline M dosing, subjects received, in a random order, each of three treatments for five repetitions of each treatment: M dosing every 24 hours, T dosing (triple M dose every 72 hours), and QN dosing (quintuple M dose every 120 hours). In the latter two conditions, subjects received placebo on the interposed days. Subjects were also exposed once to an M dose followed by four days of placebo and once to a T dose followed by four days of placebo. Study participation was contingent upon opioid abstinence and daily attendance. No observer-rated withdrawal was noted during the QN dosing regime, but observer-rated withdrawal was evident 96 and 120 post M and T. Subjective ratings of withdrawal increased linearly across days since last active dose in all conditions, including the QN conditions. In a second, ongoing study, subjects (n=5) are exposed to M, T, and QN dosing regimes in an open manner and then choose between the dosing schedules. While two subjects have chosen QN dosing over M dosing, no subjects have preferred QN over T dosing. Thus, preliminary results of this study suggest that quintuple buprenorphine doses may not abate subjective withdrawal complaints for five days in opioid-dependent outpatients and this is not a preferred dosing schedule.

FIRST CLINICAL EXPERIENCE WITH BUPRENORPHINE-NALOXONE COMBINATION SUBLINGUAL TABLET

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A non-abusable form of buprenorphine, able to be prescribed outside the methadone clinic setting, may be uniquely advantageous compared to methadone and LAAM. NIDA and Reckitt and Colman have jointly undertaken to develop a buprenorphine-naloxone combination tablet with low abuse potential. As part of the planning for a multicenter trial, this 6-week pilot provided the first clinical assessment of the safety and feasibility of two induction schedules and a preliminary estimate of the optimal dose. Twenty-five (25) subjects were inducted on either a 4 mg (n=16) or an 8 mg (n=9) dose, which was increased daily (from 4 to 8 to 16 mg) until the maintenance dose of 4 mg (n=5), 8 mg (n=11), or 16 mg (n=9) was attained. Subjects tolerated the combination tablet well, although there were more early dropouts among subjects inducted at 8 than at 4 mg (33.3% vs 18.5%). The higher maintenance dose group provided more drug-free urine samples throughout the trial (TES_{4mg}=0.2, TES_{8mg}=3.0. TES_{16mg}=5.2). These results suggest that inducting patients at a low dow and then increasing the dose may optimally reduce illicit opiate use.

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QUADRUPLE BUPRENORPHINE DOSES MAINTAIN OPIOID-DEPENDENT OUTPATIENTS 96 HOURS WITH MINIMAL WITHDRAWAL

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Three studies compared 24-, 48-, 72-, and 96-hour buprenorphine (BLIP) dosing schedules in opioid-dependent outpatients. 14 subjects receiving BLIP (sublingual maintenance (M) doses: n=5, 4 mg/70 kg; n=9, 8 mg/kg) have completed a double-blind, placebo-controlled, cross-over trial. Following baseline M dosing, subjects received, in a random order, each of four treatments for five repetitions of each treatment: M dosing every 24 hours, D dosing (double M dose every 48 hours), T dosing (triple M dose every 72 hours), and Q dosing (quadruple M dose every 96 hours). In the latter three conditions, subjects received placebo on the interposed day(s). Study participation was contingent upon opioid abstinence and daily attendance. Measures of opioid agonist and withdrawal effects were assessed daily. No observer-rated withdrawal was noted in any of the conditions. Agonist effects did not occur, and subjects could not differentiate D, T, and Q doses. Subjective withdrawal effects increased linearly across days since last active dose, but magnitude of withdrawal was minimal. In a second study, fifteen subjects received these same treatments in open conditions. Subjective, but not objective, reports of withdrawal increased in the Q condition. Subjects who completed the open dosing study were invited to participate in a subsequent study in which they choose amongst the four dosing schedules. 85% of the subjects chose the Q over the M schedule, and 46% chose the Q schedule over all dosing schedules: M, D, and T. These results suggest that BUP can be administered safely and effectively on a twice per week basis (i.e., a Q on Mondays and T on Fridays). This dosing regime allows time off from the clinic without the risk of diversion of take-home medication.

ABSTINENCE AND OCCURRENCE OF WITHDRAWAL SYMPTOMS IN METHADONE FAILURE PATIENTS CONVERTED TO LAAM

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For many opioid dependent patients, the use of methadone fails to produce consistent abstinence. This study was designed to test whether the use of Levo-Alpha-Acetylmethadol (LAAM) can be an effective treatment alternative to methadone. If LAAM is an efficacious treatment alternative, opioid use should decrease relative to treatment with methadone. Based on the pharmacokinetic differences between methadone and LAAM, withdrawal symptoms (WS) are likely to be the same or greater when patients are converted to LAAM. To explore these hypotheses, twenty-four heroin dependent Veterans receiving outpatient services at the Hines VA Hospital were assessed while on methadone and then again while on LAAM. Patients were designated as methadone failures secondary to their continued illicit opioid use despite treatment. Opioid use during the last month of methadone was compared to use during the first month of treatment with LAAM. Self-report measures of opioid withdrawal were taken during the last week of treatment of methadone and four times while on LAAM (2, 4, 8 and 28 days of treatment). Results showed that opioid use decreased significantly while on LAAM ($t=3.20$; $p<0.004$). The average opioid use while on LAAM was two times less than use while on methadone ($M=10.56$ days vs. 18.67 days). Self-reports of opioid WS also showed a significant decrease across time ($F=4.96$, $p<.01$). Planned comparisons examined WS reported while on methadone to those reported while on LAAM. These comparisons showed that by the end of 28 days treatment with LAAM, WS were significantly less than those while on methadone ($M=69.33$ vs 88.50, by modified OWS). Levo-Alpha-Acetylmethadol appears to be an effective treatment alternative for methadone failure patients.

CRA FOR THE TREATMENT OF COMBINED OPIOID AND COCAINE DEPENDENCE

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To evaluate the Community Reinforcement Approach (CRA) for the treatment of combined opioid and cocaine dependence, we 1) compared outcomes for subjects maintained on daily buprenorphine (12-16 mg SL) or methadone (65-90 mg PO) treated with CRA in a current trial (n=57) or with relapse prevention drug counseling (DC) in a prior trial (n=83), and 2) compared levels of engagement in CRA activities for CRA-treated patients who did and did not achieve periods of sustained abstinence from illicit opioids, cocaine, or both. There were no significant baseline differences between the DC and CRA groups in sociodemographic or clinical features. While rates of opioid- and cocaine-positive urine samples declined during treatment for both conditions, there were no significant differences between CRA and DC in treatment retention or rates of opioid- or cocaine-positive urine samples. For CRA-treated subjects, abstinence was significantly correlated with both the number of recreational, vocational, and social activities and number of hours engaged in these activities. Mean (SD) number of hours engaged in CRA activities for patients abstinent from illicit opioids for 3 or more consecutive weeks (n=11) compared to those never abstinent (n=13) were 198 (176) and 11 (19), with a median of 162 and 0 hours, respectively. These results support the efficacy of CRA in populations outside of Vermont, especially for patients who engage in CRA activities, and point to the importance of specifying differences in treatment and evaluating treatment process in studies of behavioral treatment.

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INTEGRATION OF LAAM INTO AN OPIATE SUBSTITUTION TREATMENT PROGRAM

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LAAM was added to the NYVA formulary in July 1994. Between September 1994 and March 1995, new patients were offered the option of LAAM or methadone. 11 of 55(20%) chose LAAM, reported satisfaction with treatment, and discontinued opiate use. Consequently, to minimize methadone diversion in a 5 day maintenance program, starting in April 1995, after a program of patient and staff education, all new patients were inducted on LAAM. In January 1996 we evaluated four groups of patients at the Clinic: (1) 17 individuals admitted to LAAM April-December 1995 with no previous methadone experience, (2) 18 individuals admitted to methadone treatment October 1994-March 1995, (3) 19 patients admitted to LAAM previously maintained on methadone and (4) 40 patients maintained on methadone. Patients on LAAM and on methadone reported decreased opiate craving and discontinued use at approximately similar rates. 11% of LAAM patients purchased street methadone vs 17% of methadone maintained patients. Patients previously treated with methadone reported a 72% preference for LAAM over methadone, 90% reporting not "feeling" a dose of LAAM the way they "felt" methadone, and 75% stating LAAM would be difficult to sell on the streets. A review of random urine drug screens for a 6 month period demonstrated that 46% of LAAM patients use cocaine intermittently and 6% chronically, while 15 % of the methadone patients use cocaine intermittently and 52% of the methadone group were found positive for cocaine on every urine drug screen. A significant proportion (54%) of patients on methadone maintenance report they would transfer to a different program if required to take LAAM. Staff report satisfaction with LAAM as a treatment for heroin dependence.

VULNERABILITY FACTORS IN OFFSPRING OF ALCOHOLIC PARENTS

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Background: Family history of alcoholism has been demonstrated to be a strong risk factor in the development of alcohol abuse and dependence. Offspring of alcoholics are 3-5 times more likely to develop alcoholism than offspring of nonalcoholics (Merikangas et al., 1994). There is inconsistent evidence indicating that anxiety disorders act as mediators of this association. **Methods:** One of the aims of the Early Developmental Stages of Psychopathology (EDSP) research program, a prospective general population study, is to identify mechanisms of familial transmission in alcohol use disorders. In the initial wave of data collection, N=3021 adolescents and young adults aged 14-24 in the greater Munich area were interviewed between February and July 1995 using the standardized interview M-CIDI (Münchner Composite Diagnostic International Interview), an adaption of the WHO-CIDI based on DSM-IV. Questions regarding parental problems with alcohol use and treatment thereof were added. **Results:** Using a community sample, we confirmed findings of family studies showing excess risks for alcohol dependence and alcohol abuse among probands reporting parental alcohol problems. Several anxiety disorders, affective syndromes, other substance use disorders and eating disorders were also associated with parental alcohol problems. Anxiety disorders preceeded alcohol use disorders in 90% of comorbid probands. The questions regarding parental alcohol problems might facilitate response bias towards severe and more recent cases. However, the proportion of alcohol problems for any parent (reported by 15% of probands) suggests satisfying validity.

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ASSESSING SUBSTANCE USE/ABUSE AMONG HIGH-RISK ADOLESCENTS IN THERAPEUTIC COMMUNITIES: POST-TREATMENT OUTCOMES

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Assessment of substance use/abuse and evaluation of the impact/effectiveness of substance abuse treatment programs require reliable data. However, much of the data used for this assessment are often self-report, potentially biased towards 'looking good', and thus, are unreliable. Additionally, procedural techniques related to collecting data on adolescent substance abusers, especially those who are juvenile offenders and have been remanded to treatment may hinder the process. Issues such as confidentiality requirements related to minor status, mistrust towards interviewers who are often suspected as 'allies' to the legal authorities, and implicit incentives to overreport treatment success and underreport substance abuse and related criminal activities (by clients as well as who know them) are some of the reasons for this difficulty. This study reviews strategies for collecting reliable data on substance use/abuse among high-risk adolescents in residential therapeutic community (TC) treatment programs for substance use/abuse problems. Post-treatment outcome findings will be used to illustrate these strategies. Data have been collected at six TCs for adolescents located in the eastern U.S. and Canada. The research subjects include clients who completed interview batteries both at admission and at 1-yr post-treatment follow-up (N<> 500). Preliminary findings indicate that the use of substances such as inhalants, hallucinogens, and methamphetamines declined significantly during the post-treatment period. Other risk behaviors associated with substance use/abuse such as involvement in criminal activities, negative peer-network structure, and school problems also reduced to a great extent. Issues concerned with ensuring reliability of data, the use of self-report, collection of hair and urine specimens, and review of Criminal Justice Systems records and other collateral information will be discussed. ACKNOWLEDGEMENT: Supported by the National Institute on Drug Abuse, Grant # 5 P50 DA07700.

ADULT SEROTONERGIC CORRELATES OF CHILDHOOD TRAUMA IN ALCOHOLICS AND COCAINE ADDICTS

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A history of childhood abuse is a common feature in substance abusers, however little is known about the biological correlates of maltreatment. Using the Childhood Trauma Questionnaire (Bernstein *et al.* 1994), a valid and reliable self- report instrument to assess the magnitude of several types of childhood trauma, we examined the associations of the levels of self-reported childhood physical and sexual abuse with markers of central nervous system serotonin activity: the prolactin, cortisol and temperature responses to challenge with meta-chlorophenylpiperazine (MCPP) in male treatment-seeking alcoholics (n=14) two weeks after completion of a medical detoxification and in cocaine addicts (n=15) two weeks after admission to an inpatient rehabilitation unit. In the alcoholics, childhood physical abuse was associated inversely with the cortisol response to MCPP (ß= -.52, t = - 2.02, p<.04). However, in the cocaine addicts, childhood physical abuse was positively associated with the cortisol response (ß = .44, t = 1.69, p<.06) and the prolactin response to MCPP (ß = .48, t = 1.90, p<.04). In contrast to physical abuse, the level of self-reported childhood sexual abuse was positively associated with the cortisol response to MCPP in the alcoholics (ß = .72, t = 3.47, p<.003), but inversely associated with the cortiso1 response in the cocaine addicts (ß = -.38, t = - 1.50, p<.08). When the levels of physical abuse and sexual abuse were adjusted for the variance common to both variables, the respective associations with the cortisol response to MCPP were increased. The pattern of association between serotonergic activity and childhood trauma depends on the type of trauma, the predominant substance dependency and the specific neuroeffector system. **References:** Furnished upon request of senior author.

A TWO-ITEM CONJOINT SCREEN FOR ALCOHOL AND OTHER DRUG PROBLEMS

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Although use of drugs other than alcohol and nicotine is fairly common among American adults, the currently recommended screens for substance use disorders (SUD's) focus only on alcohol. Previously described drug abuse screening questionnaires lack the brevity and accuracy required for routine use in primary care settings. This study, funded by the National Institute on Drug Abuse, reports on the criterion validity of a two-item conjoint screen for alcohol and other drug abuse or dependence for a primary care sample. A random sample of 434 primary care patients of ages 18 to 59 responded to nine screening items, which were produced by a focus group process. A validated diagnostic interview, the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM), based on DSM-III-R diagnoses, served as the criterion standard for SUD's. An 87.9% response rate was attained. Almost two-thirds (64.5%) of the subjects were women, and 16.4% represented ethnic or racial minorities. At least one positive response to two items, "In the last year, have you ever drank or used drugs more than you meant to?" and "Have you felt you wanted or needed to cut down on your drinking or drug use in the last year?', discriminated current SUD's with approximately 81% sensitivity and specificity. The two-item conjoint screen was 96.4% sensitive to SUD's involving two or more substances. Zero, one, and two positive responses predicted 7.4%, 45.0%, and 75.0% probabilities of a current SUD, respectively. Data collection will continue to a total of 1300 subjects, and a two-week, test-retest reliability study will be conducted. If these preliminary results hold true, then more than 80% of young and middle-aged patients with current SUD's could be recognizable by a two-item conjoint screen which is easily integrated into a clinical interview.

AN EVALUATION OF A MODEL OF PSYCHOSOCIAL FACTORS THAT MEDIATE THE RELATIONSHIP BETWEEN SEXUAL ABUSE AND ALCOHOL USE

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The study evaluated an hypothesized theoretical model of psychosocial factors that mediate the relationship between sexual abuse and alcohol use. Questionnaires containing items assessing psychosocial factors of sexual abuse, self-esteem, social support, negative beliefs, avoidance coping methods and alcohol use were administered to 237 undergraduate subjects during a class period. A series of path analyses were conducted to assess the theoretical model and to explore the direct and indirect relationships among sexual abuse, psychosocial factors, and alcohol use. The results support the hypotheses that sexual abuse is directly related to negative social support, low self-esteem, avoidance and affective beliefs; and it is also indirectly related to alcohol use. An exploratory path analysis was conducted among sexual abuse, psychosocial factors, and cigarette smoking. The results support that sexual abuse was directly related to negative social support, low self-esteem, avoidance beliefs, affective beliefs, and avoidance coping methods; and it is also indirectly related to cigarette smoking. A one-way ANOVA demonstrated significant differences between subjects with a history of sexual abuse and those without a history of sexual abuse in the use of avoidance coping methods. This finding further supports the-hypothesis that individuals with a history of sexual abuse may cope with the abusive experience by employing avoidance coping methods of drinking and smoking. Implications from these findings suggest a theoretical paradigm may be necessary for understanding the nature of alcohol and nicotine use a avoidance coping methods for negative psychosocial factors.

DEVELOPMENT OF A SEMI-STRUCTURED INTERVIEW TO ASSESS SEVERITY OF DSM-IV AND ICD-10 SUBSTANCE DEPENDENCE

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The Substance Dependence Severity Scale (SDSS) was developed to assess severity of DSM-IV and ICD-10 substance dependence across a range of substances. The SDSS is the first semi-structured clinical interview specifically developed to (a) assess the severity of drug disorders keyed to DSM-IV and ICD-10 criteria and (b) be sensitive to changes in clinical status. Consisting of items modified from the Psychiatric Research Interview for Substance and Mental Disorders (PRISM; Hasin *et al.,* in press), a semi-structured interview that provides reliable diagnoses of substance use and other mental disorders, the SDSS provides continuous severity ratings of each DSM-IV and ICD-10 Dependence, Abuse, and Harmful Use criterion within a past 30-day time frame. Test-retest pilot testing was conducted with nine current drug users assessed at intake at an urban outpatient drug treatment program. Analyses indicated excellent reliability for overall SDSS alcohol and cocaine dependence scores (Intraclass correlation coefficients = .96 and above for DSM-IV and ICD-10 dependence). These preliminary results suggest that further psychometric testing of the SDSS is necessary and worthwhile. Plans for such testing, as well as research and clinical applications, will be discussed.

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TEMPORAL PROGRESSION OF ALCOHOL DEPENDENCE SYMPTOMS IN THE US POPULATION: RESULTS FROM THE NATIONAL COMORBIDITY SURVEY.

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Background: General population data were used to determine whether a consistent temporal progression exists in the onset of symptoms building up to alcohol dependence (AD) and, if so, to study age, sex, and cohort differences in this progression. Methods: The data are from the US National Comorbidity Survey. Symptoms were assessed using a revised version of the Composite International Diagnostic Interview, the UM-CIDI, among non-institutionalized persons 15-54 years of age living in the 48 coterminous United States including students living in campus housing. Age of onset reports were obtained retrospectively. Symptom classes were estimated with Latent Class Analysis (LCA). Age, sex, and cohort differences in symptom progression were investigated with discrete-time survival analysis. Results: A four-class LCA solution was found to fit the data indicating a temporal progression of symptoms beginning with role impairment and hazardous use, moving on to tolerance and impaired control, and then to physiological dependence. Probability of initial symptom onset among alcohol users was found to be higher among people in the 10-24 age range, among men than women, and to have increased dramatically over the past four decades. Age, sex, and cohort effects were found to be less powerful in predicting symptom progression. A narrowing of the sex difference in AD symptomatology over time was observed to be due largely to a convergence in initial symptom onset among men and women in the age range 10-24. Conclusions: The increasing prevalence and narrowing of the sex difference in AD are both due largely to an increase in symptom onset during the adolescent years. As initial symptoms are usually indicative of abuse rather than dependence, this means that a rise in adolescent alcohol abuse has been more important than an increase in the transition rate from abuse to dependence in explaining the growing prevalence of alcohol dependence during recent decades.

REGULATION OF GUINEA PIG BRAIN PREPRODYNORPHIN mRNA EXPRESSION BY BINGE PATTERN COCAINE ADMINISTRATION

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Previous studies in our laboratory showed that binge pattern cocaine administration (BPCA) increased preprodynorphin (Dyn) mRNA levels in the caudate putamen of the rat. We extended these studies in cocaine-treated guinea pigs. Animals were treated with: a) binge saline for 7 days (3 times daily at hourly intervals, i.p.); b) binge saline for 5 days followed by binge cocaine for 2 days (45 mg/kg/day); c) binge cocaine for 7 days. Guinea pigs were sacrificed 30 min after the third injection and levels of Dyn mRNA were determined for selected brain regions by solution hybridization RNase protection assay using a species-specific probe. Newman-Keuls post hoc test following analysis of variance with repeated measures on the caudate putamen and nucleus accumbens showed a significantly higher level of Dyn mRNA after 2 days BPCA ($p<0.05$). Most of this difference was found in the caudate putamen, where 2 days of BPCA led to a 40% higher level, $F(1,24)=5.17$, $p<0.05$. After 7 days BPCA Dyn mRNA levels were 25% higher than saline treated animals, but this did not reach significance. No significant changes in Dyn mRNA levels were detected in frontal cortex, hypothalamus, hippocampus and amygdala of the cocaine treated animals.

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EFFECTS OF COCAINE WITHDRAWAL CONDITIONS ON POMC mRNA IN RAT ANTERIOR PITUITARY

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"Binge" pattern cocaine administration (BPCA) results in a persistent disruption in hypothalamic-pituitary-adrenal (HPA) activity. The present study investigated the effects of withdrawal from chronic BPCA on the HPA axis. Method: BPCA was given to male Fischer rats in two separate rooms. In each room, cocaine rats (n=6) received daily BPCA (45 mg/kg, ip) in the morning, and control animals (n=6) received "binge" saline. After 14 days of the treatment, rats in one room were left for 10 day withdrawal without any injection. In the other room, "binge" saline was injected during 10 day withdrawal for both cocaine and saline groups. On the last day, animals were sacrificed 30 min after the last injection or at the same time point. Plasma corticosterone was measured by RIA. Pro-opiomelanocortin (POMC), corticotropin-releasing factor (CRF) and CRF-R1 receptor mRNAs in the brain and pituitary were measured, using a modified solution hybridization protection assay. Results: Plasma corticosterone was at normal basal levels in both saline groups following 10 day withdrawal. Corticosterone and POMC mRNA returned to basal levels in animals after chronic BPCA followed by no injection during the 10 day withdrawal. Chronic BPCA followed by saline injection for the 10 days of withdrawal, however, led to a significantly decreased corticosterone levels. In parallel, a significant reduction in POMC mRNA levels was found in the anterior pituitary in this group, with no changes in CRF-R1 mRNA levels. Neither POMC mRNA in the posterior pituitary nor CRF mRNA in the hypothalamus was altered. Conclusion: Injections of saline during withdrawal from chronic BPCA resulted in decreased POMC mRNA in the anterior pituitary and decreased circulating corticosterone.

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EFFECTS OF CHRONIC "BINGE PATTERN" COCAINE ADMINISTRATION ON HIPPOCAMPAL PYRAMIDAL CELL DENDRITIC MORPHOLOGY IN RATS

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Chronic stress or glucocorticoid administration produce morphological and functional changes in the hippocampus in rats characterized by dendritic atrophy in the CA3 region and spatial memory deficts, respectively. Cocaine is a pharmacological stressor which activates the hypothalamic-pituitary-adrenal (HPA) axis leading to increased corticosterone levels which may contribute in the behavioral symptomatology in cocaine abuse. Recent data suggest that the structure and function of the hippocampus, a key structure in the adaptive brain processes such as learning and memory, may be compromised by cocaine leading to cognitive deficits. Therefore, cocaine-induced structural changes in the hippocampus were examined. Body and organ (adrenal gland, spleen, thymus) weights were measured. Cocaine-traeted rats showed significantly less weight gain and adrenal hypertrophy compared to saline-treated controls. Chronic cocaine administration significantly decreased the number of branch points ($p<0.05$) and the total length ($p<0.01$) of apical dendrites compared to saline-treated controls in our preliminary analysis when a morhologically non-selected group of CA3 pyramidal cells were included. However, no significant difference was found when (i) CA3 pyramidal neurons were pre-selected on the basis of their morphological features and (ii) the sample was balanced for the ratio of each neural phenotype. These data suggest that chronic binge pattern cocaine administration is different than chronic restraint stress with respect to their effects on hippocampal neuronal morphology. Although chronic cocaine administration seems to be a stronger stressor judged on the basis of adrenal weight, no changes were found in hippocampal morphology. Whether the absence of changes in dendritic morphology in cocaine-treated rats is due to the lack of atrophy or that what we see are only the surviving normal neurons after cocaine-induced cell loss, remains to be determined.

FUNCTIONAL SELECTIVITY AT THE D_2 DOPAMINE RECEPTOR: STUDIES IN TRANSFECTED MN9D CELLS.

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The capacity to increase synaptic concentrations of dopamine is thought to be the primary cause of the reinforcing effects of cocaine and possibly some amphetamine-like drugs. Thus, the ability to selectively activate pre- and postsynaptic dopamine receptors could be a useful tool in the treatment of individuals abusing these drugs. This study is directed toward the development of pre- and postsynaptic-selective D_2 receptor agonists using a family of compounds we have developed. The full intrinsic activity D_1 agonist dihydrexidine (DHX), while ten-fold D_1 selective, also has high affinity for the D_2 receptor ($K_{0.5}$ = 100 nM in rat striatum). In rat brain preparations, DHX has an unusual D_2-like functional profile, having agonist properties at functions mediated by "postsynaptic" D_2 receptors (e.g., inhibition of adenylyl cyclase activity in striatal slices), but no agonist effects in D_2-mediated "presynaptic" functions (e.g., inhibition of nigral cell firing, or inhibition of dopamine synthesis or release). Yet DHX binds with similar affinity to both pre- and post-synaptic receptors. The present study investigated the functional selectivity of DHX and certain analogs using MN9D cells, a clonal mesencephalic-derived line that can synthesize and release dopamine (making it a model of dopamine neurons). MN9D cells stably transfected with the D_2 receptor were used. DHX, N-n-propylDHX, and 4-methyl-N-n-propylDHX had ca. 100-fold lower affinity in the D_2-MN9D line than at D_2-like sites in rat striatum. The D_2 agonists quinpirole and R(-)NPA inhibited the stimulated release of [^{3}H]dopamine by 70% and 60%, respectively, at 10 μM. Neither DHX nor N-n-propylDHX inhibited stimulated [^{3}H]dopamine release significantly even at concentrations as high as 10 μM. These data are consistent with previous reports that DHX and N-n-propylDHX do not inhibit dopamine release in rat brain (assessed *in vitro* or *in vivo*). Together, the data suggest that members of this class of compounds may have "functional selectivity" for D_2-like receptors, having agonist or antagonist functional properties depending on the transduction machinery associated with the receptor.

ELECTROPHORETIC EFFECTS OF DAMGO ON GLUTAMATE-DRIVEN AND FIMBRIA-DRIVEN NEURONS IN NACC SHELL

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The reinforcing actions of opiates in the NAcc appear to be regulated by both a DA-dependent (VTA) and a DA-independent (NAcc) mechanism. Consistent with this notion, our electrophysiological studies in vivo suggested that the effects of systemically administered opiates on NAcc neurons in the core must occur through both the VTA dopaminergic projection to the NAcc, as well as directly within the NAcc. Here we report data from our studies characterizing the electrophoretic effects of ID-Ala^2,NMe-Phe^4,Gly-ol]-Enkephalin (DAMGO), a selective μ agonist, on glutamate- and hippocampal-driven NAcc neurons in the shell of anesthetized Sprague-Dawley rats. Our results show that electrophoretic application of DAMGO (1.0 mM) into the NAcc-shell suppressed glutamate-driven activity ($p<0.0001$). In contrast, the present data suggest that local DAMGO had little effect on fimbria-driven NAcc-shell neurons ($p>0.05$). These findings suggest that systemic administration of opiates suppresses the activity of NAcc neurons in the shell directly via μ receptors. However, our results suggest that both local and extra-NAcc regions regulate the effects of opioids on excitatory afferent inputs to the NAcc. For instance, we found that the inhibition of timbria-driven NAcc-core neurons by microinfusions of morphine into the VTA is reversed by systemic administration of heroin. This suggests that systemic administration of opiates acts on other brain regions to counteract the inhibitory effects of opiates on NAcc activity elicited from the VTA alone. It has not been determined if these multiple effects of opiates on NAcc physiology also involve neurons in the shell. The results from this ongoing study may contribute to our understanding of the interactions of opiates with DA and non-DA mechanisms modulating NAcc function.

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OPIOID EFFECTS ON PREFRONTAL CORTICAL NEURONAL ACTIVITY AND EXCITATORY RESPONSE

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Medial prefrontal cortical (mPFC) circuitry has been proposed to play a significant role in behavioral reinforcement, and therefore, activity of the mPFC neuronal population should be modified by exposure to drugs of addiction. As mu opioids can mediate reinforcing effects of heroin in the rat, we have examined the effects of predominantly mu receptor-selective opioids on the firing of mPFC neurons. Because opioid mediation of mPFC activity may involve alteration of endogenous excitatory systems, we also have evaluated the interactions of opioids and both excitatory neurotransmitters and afferent-driven activity. Our previous work in halothane-anesthetized rats revealed there opioids in terms of their effects on mPFC response to electrophoretically applied acetylcholine (ACh) and glutamate (Glu). Systemic morphine attenuates Glu-induced excitation in the majority of cells; DAMGO attenuates the Glu response in approximately half of the cells. ACh-induced excitation is unaltered by opioids. In addition, administration of systemic morphine decreases mPFC evoked activity following stimulation of either mediodorsal thalamus or basolateral amygdala in the majority of cells studied to date. Further studies are needed to assess the ability of naloxone and more specific opioid antagonists to block these effects.

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OPIOID-INDUCED EFFECTS IN THE RAT VENTRAL PALLIDUM: INTRA- AND EXTRACELLULAR RECORDINGS.

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The ventral pallidum (VP) is a brain region rich in opioids and is thought to be involved in reward ***mechanisms.*** We recently have undertaken several studies to evaluate the physiology of VP opioids. Activity of 233 single VP neurons was measured extracellulary in chloral hydrate-anesthetized rats. Morphine (i.v.) decreased neuronal firing with an ED50 of 1mg/kg. Microiontophoretic applications produced both increases and decreases in firing. In contrast, when only VP neurons that were postsynaptic to the nucleus accumbens were evaluated, morphine-induced excitations predominated. Naloxone antagonized these responses. Iontophoresis of DAMGO inhibited firing almost exclusively. U50488H also suppressed firing, whereas DPDPE produced both excitations and inhibitions. Often, morphine was able to increase firing of the same neuron that decreased activity with DAMGO. When morphine (10μM) was applied to the bath surrounding basal forebrain slices, intracellular recordings of VP neurons revealed a hyperpolarization (5±0.9mV) in 20 of 29 neurons tested. This was reversed by naloxone. These data suggest that when the neuronal circuit of the recorded cells is exposed to opioids, VP cells are hyperpolarized (*in vitro* study) and firing rate decreases (i.v. morphine *in vivo*). However, more circumscribed (microiontophoretic) application of opioids yields both rate increases and decreases. These differences may reflect the activation of different opioid receptor subtypes, differences among subpopulations of VP neurons and/or specific presynaptic effects on a secondary transmitter. For example, opioid-induced excitations of VP neurons postsynaptic to the accumbens may reflect an inhibition of GABA. Work supported by DA05255 to TCN.

CHARACTERIZATION OF NOVEL N,N'-DISUBSTITUTED PIPERAZINES AS POTENTIAL IRREVERSIBLE AGENTS FOR SIGMA RECEPTORS

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Sigma receptors have been implicated in many physiological and behavioral functions including regulation of motor behavior, learning and memory, and NMDA, muscarinic and dopamine receptor modulation. Research on sigma receptors has resulted in a significant increase in the development of highly selective sigma ligands. The development of ligands for labeling receptors in cells and membrane fractions has proven useful in defining the role of sigma binding sites. A series of aryl piperazines such as compound 1 has been shown to exhibit high affinity for sigma- 1 and sigma-2 subtypes (Soc. Neuroscience Abstr. 21: 1610, #631.11, 1995).

Isothiocoyanate (4) and azido (5) derivatives were synthesized from the amine (3) via the nitro (2) precursor. All four compounds exhibited high sigma- 1 and sigma-2 affinity, with Ki = 0.25 nM - 17.6nM. Compounds 4 and 5 will be investigated as receptor alkylating and photoaffinity probes, respectively, using compounds 2 and 3 as controls. These data will be discussed.

MORPHINAN CYCLIC IMINES AND PYRROLIDINES: HIGH AFFINITY, "IRREVERSIBLE" OPIOID AGONISTS

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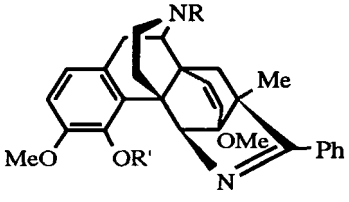
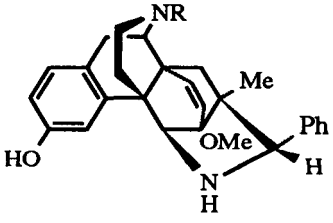
As part of our continuing search for new treatments for opiate abuse, we prepared analogs of the cyclic imine **1** (R=Me, R'=H) which had earlier been shown to have potent antinociceptive activity. It was envisioned that the conformationally constrained phenyl group in this and close analogs would confer μ selectivity. In displacement binding assays in guinea pig brain membranes, ligands of structure **1** showed high affinity and significant selectivity for μ receptors. Analogs (**2**) lacking a C_4-OH or -OMe group had even higher affinity but were not selective. In guinea pig *ileum* all the morphinans showed potent agonist activity (IC_{50} 0.1-4 nM) but could not be antagonized by selective μ and κ antagonists, nor washed out of the tissue. They were less potent agonists in mouse *vas deferens* (IC_{50} 1-40 nM) and some were antagonized by naltrindole (δ). Ligands of both structure **1** and **2** (R=Me) were shown to fit a model developed from potent *in vivo* μ agonists. Thus a series of potent, high affinity ligands have been prepared that add to the range of 1ipophilic/"irreversible" opioid agonists.



R=Me, CPM
R'=H, Me



1 **2**

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MORPHINE MODULATES GABA- AND GLUTAMATE-EVOKED RESPONSES IN VENTRAL PALLIDAL NEURONS

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The possible modulatory influence of morphine on GABA- and glutamate-evoked responses in the ventral pallidum (VP) was investigated using microiontophoretic techniques. Neurons were recorded extracellularly from chloral hydrate-anesthetized rats. Morphine modulation of amino acids was determined by comparing the ratio of the changes in amino acid-evoked activity ("signal") to spontaneous activity ("noise") in control (amino acid alone) and test (amino acid plus morphine) conditions. An ejection current-response curve (1 to 128 nA) was generated to determine the current level which produced 50% of the maximum morphine-induced response (ECur50) and one that did not alter baseline firing rates (SubTh). Of the 78% (65/83) of VP neurons sensitive to morphine application, 49 neurons displayed an increase in firing rate whereas 16 neurons showed a decrease. Co-iontophoreses of ECur50 morphine with GABA or glutamate typically resulted in an attenuation of the amino acid signal-to-noise ratio (5/12 and 9/14, respectively), although potentiations were observed (1/12 and 4/14, respectively). Interestingly, SubTh morphine also attenuated (7/17 and 6/16, respectively) and potentiated (3/16 and 7/16, respectively) the amino acid signal-to-noise ratio. These changes were independent of any drug-induced changes in spontaneous firing rate. Recently, VP GABA activity has been shown to influence sensorimotor gating, as measured by prepulse inhibition. Therefore, the ability of morphine to modulate amino acid signals in the VP may play an important role in the integration of sensorimotor information. For example, dysfunction of this modulatory feature may be involved in the expression of psychological "cravings" associated with drug abuse. Work supported by USPHSGs DA05651 to PIJ and DA05255 to TCN.

SYNTHETIC APPROACHES TO DERIVATIVES OF THE δ-SELECTIVE OPIOID ANTAGONIST NALTRINDOLE

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The opioid receptors (μ,κ,δ) and their subtypes are involved in the various aspects of the perception of pain, pleasure and mood as well as regulation of immune function. The development of selective opioid receptor ligands offers the potential for improving clinical treatments involving these systems. Research has demonstrated that naltrindole, a delta selective antagonist, blocks under some conditions the reinforcing properties of cocaine and prevents the development of drug tolerance and dependence to morphine. Synthesis of potent non-peptidic selective ligands would also provide valuable research tools for further study of the structure and function of delta opioid receptor systems. Previous work has shown that a 5ß-methyl group can have a major influence on the pharmacology of opioids, specifically increased binding affinity and agonist potency. Other studies have shown that 14-alkyl groups also have a major influence on the pharmacology of opioids; 14ß-ethyl morphinone was shown to display many thousand times the agonist potency of morphine. A series of indole analogs (both potential agonists and antagonists) was therefore prepared with substitution at either C-5 or C-14 to determine the influence of such groups in the indole series. Preliminary results show that the 5-methyl oxycodone indole series had no appreciable affinity or selectivity for any of the opioid receptors. 14-Isopentylhydromorphone indole displayed lower binding affinity for both μ and δ receptors compared to hydromorphone indole, but μ/δ selectivity was essentially unchanged indicating that this position can tolerate large changes in functionality without loss of selectivity.

SUBSTITUTED AMIDE DIPHENYLMETHYLPIPERAZINES AS NOVEL DELTA OPIOID RECEPTOR AGONISTS

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Recent studies of opioid receptor subtypes have revealed new physiological functions of the delta receptor and suggest that delta agonists constitute a novel class of analgesics and immuno-modulators. In a previous paper, we described a highly selective delta agonist SNC80, (+)4-[(αR)-α-{(2S, 5R)-4-allyl-2,5-dimethyl-1-piperazinyl}-3-methoxybenzyl]-N, N-diethylbenzamide [S. N. Calderon *et al.;* J. Med. Chem. 37, 2125, 1994]. As a part of our continuing program to develop novel delta ligands, we have pursued chemical modifications of SNC80 to clarify the importance of the amide group. Among the compounds obtained, the N-methyl-N-ethylbenzamide derivative showed higher selectivity for the delta receptor than SNC80 (μ /δ ratio = 1755 and 857), although its affinity for the delta receptor was somewhat less than that of SNC80 (IC_{50} = 4.2 nM and 2.9 nM). Compounds with one or both ethyl groups removed from the amide group on SNC80 showed 50-fold and 150-fold weaker affinities for the delta receptor, respectively. Both meta and ortho amide positional isomers of desmethoxy-SNC80 also exhibited remarkable, 90-fold and 2500-fold, decrease in activities. Thus, given that the binding affinity for the delta receptor was dramatically changed by the character of the amide group, we propose that the amide function is one of the active binding sites for the delta receptor in this diphenylmethylpiperazine series.

MECHANISMS OF μ-OPIOID AGONIST EFFICACY STUDIED USING RECEPTOR-STIMULATED [^{35}S]GTPγS BINDING

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Stimulation of [^{35}S]GTPγS binding by full and partial μ-opioid agonists was examined in SK-N-SH cell and rat thalamic membranes. The u-selective agonist DAMGO stimulated [^{35}S]GTPγS binding maximally by 220 and 165% in SK-N-SH and rat thalamic membranes, respectively. DAMGO was a full agonist in both systems, whereas morphine and fentanyl were partial agonists of relatively high efficacy, producing about 55-70% of the maximal stimulation produced by DAMGO. Buprenorphine was a partial agonist of low efficacy (10-15 % of DAMGO-stimulation). In both SK-N-SH and rat thalamic membranes, the differences in efficacy among the four agonists was dependent upon the GDP concentration, with increasing GDP magnifying the diferences in efficacy. Scatchard analysis of agonist-stimulated [^{35}S]GTPγS binding in SK-N-SH membranes revealed that agonist efficacy was correlated both with the apparent affinity of the receptor-coupled G-proteins for [^{35}S]GTPγS (KD) and with the number of G-proteins activated by the agonist-occupied receptor (B_{max}). However, K_D differences were only significant between buprenoiphine and the higher efficacy agonists, whereas B_{max} differences were also significant between DAMGO and morphine or fentanyl. Chronic (24 hr) treatment of SK-N-SH cells with the four agonists indicated that the degree of desensitization did not completely correlate with agonist efficacy, with buprenorphine producing nearly as much desensitization as DAMGO, and morphine producing less desensitization than either DAMGO or buprenorphine. These results suggest that differences in μ opioid agonist efficacy result from differences in the receptor-mediated activation of G-proteins, measured as differences in both the number and affinity of activated G-proteins, and that there may be a complex relationship between agonist efficacy, potency and receptor desensitization.

ACKNOWLEDGEMENTS:

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EFFECTS OF CHRONIC MORPHINE TREATMENT ON MU OPIOID-STIMULATED [^{35}S]GTPγS AUTORADIOGRAPHY

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Chronic opiate administration results in tolerance and dependence, but the regulation of mu opioid receptor function during this process is not clearly understood. Mu opioid agonist-stimulated [^{35}S]GTPγS *in vitro* autoradiography was performed to localize changes in mu opioid receptor-coupled G-protein activity in brain after morphine treatment. Rats were treated for 12 days with increasing doses (10-320 mg/kg/day) of morphine. Control rats were injected either with saline or a single acute injection of morphine (20 mg/kg). Mu opioid-stimulated [^{35}S]GTPγS binding was measured by autoradiography of brain sections in the presence and absence of the mu opioid agonist DAMGO. No significant changes were detected in basal or agonist-stimulated [^{35}S]GTPγS binding in brains from rats injected with an acute dose of morphine. In chronic morphine treated rats, however, DAMGO-stimulated [^{35}S]GTPγS binding was significantly reduced compared to control rats in the following brainstem nuclei: dorsal raphe nucleus, locus coeruleus, parabrachial nucleus and commissural nucleus tractus solitarius. No significant changes were observed in other brain regions, including the nucleus accumbens, amygdala and thalamus. These data indicate that chronic morphine treatment results in decreased mu opioid activation of G-proteins in specific brainstem nuclei involved in physiological homeostasis and autonomic function, which may have implications in the development of opiate tolerance and physical dependence.

ACKNOWLEDGMENTS:

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ACTIVATION OF THE CLONED HUMAN KAPPA OPIOID RECEPTOR BY AGONISTS ENHANCES [^{35}S]GTPγS BINDING TO MEMBRANES

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Kappa opioid receptors mediate many effects of opiates and opioid compounds. We recently cloned the human k opioid receptor. In this study, we examined effects of activation of the k receptor stably expressed in CHO cells on [^{35}S]GTPγS binding to membranes.The k opioid agonist U50,488H increased [^{35}S]GTPγS binding in a dose-dependent manner with an EC_{50} of 3 nM. Naloxone (1μM) shifted the dose-response curve of U50,488H to the right by 10 fold, indicating that this is a receptor-mediated effect. Pretreatment of the cells with pertussis toxin (100 ng/ml, 24 h) abolished the U50,488H-induced increase in [^{35}S]GTPγS binding, suggesting the involvement of G_i and/or G_o proteins. The order of potencies of opioid ligands tested in stimulating [^{35}S]GTPγS binding was dynorphine 1-17 > (±)EKC > U50,488 = tifludom = ß-FNA > diprenorphine > nalorphine > pentazocine = nalbuphine > buprenorphine. Dynorphin 1-17, (±)EKC, U50,488, tifluadom and ß-FNA were full agonists, but nalorphine, diprenorphine and pentazocine were partial agonists. Nor-BNI and naloxone were antagonists devoid of activities. For the five full agonists, EC_{50} values in stimulating [^{35}S]GTPγS binding were similar to K_i values in inhibiting binding to the k receptor. That activation of the human k receptor enhances [^{35}S]GTPγS binding provides a simple functional measure for receptor activation and can be used for determination of potency and intrinsic activity of opioid ligands on the k receptor.

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RTI-4614-4 AND ITS ENANTIOMERS DIFFER IN EFFICACY, POTENCY AND INTRINSIC ACTIVITY AS MEASURED BY STIMULATION OF [^{35}S]GTP-γ-S BINDING.

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Recent studies have revealed that the opioid agonist-mediated stimulation of [^{35}S]GTP-γ-S binding provides a "functional" measure of agonist occupation of μ-opioid receptors. The "super-potent" opiate RTI-4614-4, (±)-cis-N-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylpropanamide is a mixture of four stereoisomers [(2S,3R,4S)-1a, (2R,3R,4S)-1b, (2R,3S,4R)-1c and (2S,3S,4R)-1d]. Isomer la is the most potent compound *in vivo* and in the MVD preparation, yet has the lowest binding affinity of the four enantiomers using cloned mu receptors and mu/kappa chimeras (Lu *et al.,* this meeting). We hypothesized that la has greater intrinsic activity than the other enantiomers. We therefore measured agonist-mediated stimulation of [^{35}S]GTP-γ-S binding in HN9.10 cell membranes stably transfected with rat mu opioid receptors and determined potency (ED50), efficacy (maximal stimulation) and intrinsic activity (effect as a function of receptor occupation). In the presence of 100 μM GDP: 1) the order of potency was etorphine-1c > RTI-4614-4 >1a >1b > DAMGO > morphine, 2) the maximal stimulations were 1a (71%), 1b (153%) > 1c=DAMGO=etorphine> morphine (99%) > 1d=IOXY (0 %). The ED50 of 1a (12 nM) was much lower than its Ki value (374 nM). The receptor occupancies producing a 50% maximal response were: 1a (0.51%), 1b (49.37%) and 1c (46.95%). These data demonstrate that the four enantiomers of RTI-4614-4 differ in efficacy and intrinsic activity. We speculate that this results from binding to different domains of the mu opioid receptor (see Lu *et al.,* this volume).

EFFECTS OF METHADONE AND OTHER DRUG TREATMENT ON CYP 450 ENZYMES

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Methadone is widely used in the treatment of opioid dependence. Inhibition of CYP enzymes by methadone and/or other drug treatment may lead to drug interactions. Fifty-eight severely dependent opioid patients (mean age ± SD, yrs. = 35.4 ± 9.5, range 22-66), were phenotyped with dextromethorphan (30 mg). Twenty-eight patients received methadone treatment only (4 had completed methadone treatment before phenotyping), 23 received methadone and another drug treatment (diazepam 16, clonidine 4, antidepressants 3) and 7 patients did not receive any drug treatment. The O-demethylation (ODMR) and N-demethylation ratios (NDMR) (measures of CYP2D6 and CYP3A4 activity, respectively) were calculated. Log ODMRs of patients receiving methadone only were significantly higher ($x \pm SD = -1.59 \pm 0.7$, $p < 0.05$) than those not receiving methadone and non-dependent controls (N = 480) ($x \pm SD = -2.4 \pm 0.6$ and -2.39 ± 0.7, respectively). Methadone only produced a small shift in log NDMRs ($x \pm SD$ = methadone only: 0.71 ± 0.43; non-methadone: 0.53 ± 0.4, N.S.) and controls ($x \pm SD = 0.48 \pm 0.34$). The addition of diazepam or clonidine to methadone did not significantly change log ODMRs or NDMRs, but imipramine may further contribute to CYP2D6 inhibition (mean log ODMR ± SD = -1.26 ± 0.3). These data suggest that during clinical practice methadone treatment inhibits CYP2D6 activity, but has little effect on CYP3A4 activity.

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DYNORPHIN A (1-8) ANALOG, E-2078, IS STABLE IN VITRO IN HUMAN AND RHESUS MONKEY BLOOD

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In vitro biotransformation of dynorphin (Dyn) A (1-8) and its analog, [N-methyl-Tyr^1, N-methyl-Arg^7-D-Leu^8]dynorphin A (1-8) ethylamide (E-2078), in human and rhesus monkey blood was studied using matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). Dyn A (1-8) and its analog, 0.59 mg/ml, was each added to freshly drawn human (n = 3) and rhesus monkey (n = 3) blood incubated at 37°C. At specific timepoints, blood samples were collected. Plasma was separated from the blood by centrifugation at 4,000 rpm for 5 min. The plasma, 200 ml, was added to 1.8 ml of 1% TFA, filtered with membrane filters of M.W. cut-off of 3,000, then followed by MALDI-MS measurements. It was found that Dyn A (1-8) was processed into two major biotransformation products, Dyn A (1-6) and Dyn A (2-8). Two major cleavage sites in the biotransformation were identified, Arg(6)-Arg(7) position to form Dyn A (1-6); and Tyr(1)-Gly(2) position to form Dyn A (2-8). No C-terminal cleavage was detected. Biotransformation in rhesus monkey blood occurred at a faster rate than in human blood. Dyn A (1-8) was cleared from monkey blood in about 30 min, whereas, in human blood, Dyn A (1-8) was cleared around 90 min incubation. These results corroborate the findings in our previous studies of in vitro biotransformation of Dyn A (1-17) in human and rhesus monkey blood. Studies of Dyn A (1-8) analog, E-2078, indicate that this synthetic peptide was very stable against enzymatic cleavage in human and rhesus monkey blood. Methylation at Tyr(1) and Arg(7) positions was protective. No cleavage at Tyr(1)-Gly(2) and Arg(6)-Arg(7) positions was detected, which are the biotransformation pathways of Dyn A peptides. Minor biotransformation products, such as E-2078 (1-5), (14) and (3-6), were detected in blood of some human and rhesus monkey subjects at certain incubation timepoints. The majority of E-2078 remained intact even for a period of 24-hour incubation. Thus, E-2078 may be a suitable candidate for further pharmacological studies. **ACKNOWLEDGEMENTS:** Supported by NIDA: P50-DA 05130, DA 00049 (MJK); NIH: RR00862 (BTC); and NIDA: DA 00254 (JHW).

SPECIES DEPENDENT FORMATION OF MORPHINE-6-GLUCURONIDE (M-6-G) FROM MORPHINE

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In humans, morphine-6-glucuronide (M-6-G) is an active metabolite of morphine that may contribute to its clinical effects. We determined whether or not M-6-G is formed from morphine in mice and rats, using an HPLC-electrochemical detection method (lower limit of detection - 0.010 μg/ml). In cancer patients M-6-G can be detected in plasma within 30 min of the start of a morphine infusion and at steady-state the mean plasma molar ratio of M-6-G to morphine was 1.22. During repetitive morphine dosing to cancer patients the lumbar CSF to plasma ratio for morphine was 0.76 and for M-6-G was 0.12. Over a 100-fold range the CSF levels of M-6-G were proportional to plasma M-6-G. The animal studies included male Sprague Dawley rats that were implanted subcutaneously with three 75 mg morphine pellets and male Swiss Webster mice that were implanted with one 75 mg pellet. At 6-48 hours post-implantation, morphine, but not M-6-G, was detected in plasma and brain samples from both animal species. Our data indicate that M-6-G accumulates in human plasma and CSF but not in rat or mouse plasma or brain during continuous administration of morphine. In contrast to humans, M-6-G appears to play no role in the pharmacological effects (*e.g.,* analgesia and tolerance) seen in mice or rats given morphine.

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MORPHINAN BRAIN METABOLISM BY GENETICALLY VARIABLE CYTOCHROME CYP2D6

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For many centrally acting drugs, effective brain concentrations can be altered by the genetically and/or environmentally variable enzymes which metabolize them. These enzymes are present in the brain, where they have specific, individualized patterns of distribution and regulation. CYP2D6 is a genetically variable enzyme (lacking in 7% of Caucasians), which activates opiates, inactivates amphetamines, metabolizes tricyclic antidepressants and serotonin uptake inhibitors, and is potently inhibited by (-)cocaine. RT-PCR, catalytic drug metabolism and immunohistochemical studies were used to study CYP2D1 (rat homologue) in different rat brain regions. We found significant regional variation in CYP2D1 mRNA levels, catalytic activity and immunolocalization in rat brain (*e.g.* cerebellum displays higher levels of CYP2D1 than the frontal cortex). Female rat brains had higher levels of CYP2D1 activity than male brains. These findings indicate that there is regionally localized drug metabolism in the brain and suggest that variation in this metabolism may contribute to interindividual differences in drug response, propensity to drug dependence and/or neurotoxicity.

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L-SELECTRIDE; A NOVEL AND GENERAL O-DEMETHYLATING AGENT FOR MORPHINE ALKALOIDS AND DERIVATIVES. DIRECT AND SIMPLE COVERSION OF THEBAINE TO ORIPAVINE

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A 3-phenolic group is essential for the high binding affinity of the morphine alkaloids to the opioid receptors. As the most commonly employed starting materials for opioid synthesis are methyl ethers (codeine, thebaine), aromatic O-demethylation is a key step in the synthesis of drugs based on these alkaloids. Although this step can be problematic due to the sensitive nature of the substrates, three complimentary procedures have been developed allowing successful O-demethylation in most cases. However, each of these (BBr_3, PrSNa and KOH, the latter two at elevated temperatures) have certain disadvantages. L-Selectride was shown to be a facile, non-toxic alternative for the O-demethylation of a wide variety of opioids, including codeine, oxycodone, the thevinols and the indole derivatives. The utility of this procedure was demonstrated by performing the first direct conversion of thebaine to oripavine, a transformation which had been unsuccessfully attempted for decades. Further studies showed that L-Selectride simultaneously N-deprotected and O-demethylated opioids with a cyanamide or carbamate group, allowing a convenient synthesis of the important norphenols.

THE CYTOCHROME P4502D6 (CYP2D6) POLYMORPHISM AFFECTS ABUSE PROPERTIES OF DEXTROMETHORPHAN (DEX)

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DEX is a non-opioid antitussive metabolized by CYP2D6 to an active metabolite, dextrorphan (DOR). CYP2D6 is polymorphic in human (phenotypic extensive [EM] and poor [PM] metabolizers), and is absent in 7-10% of the Caucasian population (PM). In PMs there is little DOR production. We studied the pharmacologic effects of DEX in EMs vs. PMs. DEX doses ranged from 0 to 6 mg/kg, based on subject tolerance. Plasma kinetic data show profound differences in DEX metabolism between EMs and PMs. In EMs the major metabolite in plasma is DOR (AUC x ± SD = 43.2 ± 12.4 nmol/ml/h vs 3.9 ± 0.5 in PMs while in PMs the major component found in plasma is unchanged DEX ((AUC 3.9 ± 0.38 nmol/ml/h). DEX produced qualitatively and quantitatively different subective effects (6 EMs vs. 4 PMs). EMs reported more pleasant subjective effects and overall liking, while PMs had more negative effects and toxicity. At DEX 3 mg/kg EMs reported significantly greater "liking" ($p = 0.02$) and PMs reported greater dysphoric effects ($p = 0.03$) (Cole/ARCI scales). Several EMs had para-hallucinatory experiences. These data suggest PMs may be less likely to abuse DEX.

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3-METHYLFENTANYL CONGENERS RTI-4614-4 AND ITS ENANTIONMERS BIND TO DIFFERENT DOMAINS OF THE MU OPIOID RECEPTOR AND CHIMERIC MU/KAPPA RECEPTORS.

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To determine if mu opioid receptor agonists bind to different binding domains, we assessed the interaction of the 3-methylfentanyl congeners RTI-4614-4 and its four enantiomers with the cloned mu opioid receptor stably expressed in HEK-293 cells and μ/κ chimera receptors. Receptors were labeled with the peptide agonists [^{3}H]DAMGO and [^{3}H]DADL, the opiate agonists [^{3}H]etorphine ([^{3}H]ET) and [^{125}I]IOXY-AGO and the opiate antagonist [^{125}I]IOXY. Most test agents had considerably higher K_i values with [^{3}H]etorphine ([^{3}H]ET) than with r^{3}H]DAMGO. The "ET/DAMGO" shift was greatest for DAMGO (68-fold) and least for isomer C (6.0-fold). The enantioselectivity of the "ET/DAMGO" shift of isomers a, b, c, d was different than the enantioselectivity of their Ki values measured with [^{3}H]DAMGO. Chimera III(aa κ1-141/μ151-398) and chimera IV(aa μl - 150/κ‖142-380) bound [^{125}I]IOXY with high affinity. When the region from the N terminal to the start of the TMH3 of the μ receptor was substituted by that of the κ receptor (chimera III), affinities for most test agents were substantially decreased as compared with those of the μ receptor. The Ki(chimera III)/Ki(RMOR) shift was greatest for isomer b (590-fold) and 72-fold for isomer c. These and other data suggest that 1) peptide and alkaloid ligands bind to different domains of the mu receptor, 2) the region from N terminal to the start of the TMH3 of the mu opioid receptor is important for μ agonist selectivity and 3) enantiomers of RTI-4614-4 bind to different domains of the μ receptor.

EFFECTS OF MK-801 ON DOPAMINE RELEASE AND RECEPTOR BINDING IN THE STRIATUM OF MORPHINE-DEPENDENT RATS

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Pretreatment with MK-801, a noncompetitive N-Methyl-D-Aspartate receptor antagonist, 30 min before each administration of morphine (sc) twice a day for 7 days inhibited the development of naloxone-precipitated withdrawal symptoms in male Sprague-Dawley rats. In order to investigate the mechanism of the above effect we measured changes in dopamine release and dopamine D_1 and D_2 receptor binding characteristics in rat striatum. *In vivo* microdialysis assays showed that the decrease in extracellular dopamine concentration and the simultaneous increase in dopamine metabolite(DOPAC and HVA) concentrations in the caudate putamen that occurred during naloxone-precipitated withdrawal in rats chronically treated with morphine were significantly attenuated when MK-801 was coadministered with morphine during chronic treatment. In the binding studies using [N-methyl-^{3}H]SCH23390 and [^{3}H]spiperone as the ligands for D_1 and D_2 receptors, respectively, the Bmax and Kd values of both [^{3}H]SCH23390 and [^{3}H]spiperone in striatal membrane preparations of rats chronically treated with morphine and then treated with naloxone were not different from their respective control rats. When MK-801 was coadministered with morphine, however, the Bmax value of [^{3}H]SCH23390 binding at D_1 receptors in the striatal membrane preparations significantly increased compared with that of rats treated only with morphine, while no changes were found in Kd and Bmax values of [^{3}H]spiperone binding at D_2 receptors. These results suggest that MK-801 can inhibit the development of opioid dependence by influencing the dopamine transmission, probably by upregulating D_1 receptors in the rat striatum.

DIFFERENTIAL DOWN-REGULATION OF OPIOID RECEPTOR SUBTYPES BY BUPRENORPHINE TREATMENT.

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Previous binding studies in our lab resolved: 1) four high affinity [^{3}H]DADL binding sites in rat brain membranes depleted of μ or δ binding sites by pretreatment with BIT or (+)-trans-SUPERFIT and 2) two high affinity [^{125}I]IOXY binding sites in guinea pig membranes depleted of μ and δ binding sites by pretreatment with BIT and FIT. To test the hypothesis that these sites are different from μ receptors, we utilized a single buprenorphine (BUP) injection which has been reported to down-regulate μ receptor. Rats (5-10 each group) were sacrificed 24 hrs after BUP i.p injection. Whole-brain membrane preparations and binding assay protocols followed published procedures. Low dose BUP (0.5 mg/kg) had the following effects: μ [⇓ 50%], δ-cxl [⇓ 50%], δ- -ncx1, δ-ncx2 and δ-cx2 [no change], κ-2a and κ-2b [⇓ 40 %]. High dose BUP (2.5 mg/kg): μ [⇓95%], δ-cxl [⇓ 90%], δ-ncx1 [⇓70%], δ-ncx2 and δ-cx2 [no change], κ-2a and κ-2b [⇓ 80%]. The recovery-rate of μ, κ-2a and κ-2b binding sites was determined 1, 2, 3, 4, and 5 days after high dose BUP treatment. The times for 50% recovery were: μ [63 hr], κ-2a [41.7 hr] and κ-2b [44.5 hr]. Maximum recovery was 90% for μ receptors and 70% for κ-2a and κ-2b binding sites. Other conclusions are: 1) μ and δ-cx1 binding sites are substantially down-regulated by BUP; 2) δ-ncx2 which corresponds to the "classic" δ receptor, is not down-regulated by BUP; 3) δ-cx2, which has a δ-like ligand-selectivity profile, is not down-regulated by BUP and is different from δ-cx1; 4) κ-2a and κ-2b binding sites are down-regulated less than μ receptors, recover faster but less completely; 5) These data support the hypothesis that κ-2a and κ-2b binding sites are different from μ and δ receptors; 6) These data support the hypothesis that δ-ncx1 is different from μ and the other δ subtypes 7) Viewed collectively with other published data, these results support the hypothesis that the δ-ncx1, δ-ncx2, δ-cx2, κ-2a and κ-2b sites are distinct from μ receptors.

VISUALIZATION OF NOVEL OPIOID RECEPTOR DISTRIBUTIONS IN RAT AND GUINEA PIG BRAIN WITH THE ANTAGONIST LIGAND [^{125}I]IOXY.

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Previous studies established that the radiolabeled antagonist [^{125}I]IOXY labels κ_2 opioid receptors in membranes depleted of μ and δ binding sites with the irreversible ligands BIT (μ-selective) and FIT δ selective). These studies, which used published procedures, were undertaken to establish the anatomical distribution of opioid receptors labeled by [^{125}I]IOXY. Two assay conditions were used: 1) 50 mM TRIS-HCl, pH 7.4, 10 mM NaCl (TRIS/Na) and 2) 50 mM KPO4, pH 7.4, 400 mM NaCl (KPO4/Na). Results for rat brain. [^{125}I]IOXY labeled a mixture of μ and δ receptors using sections not pretreated with BIT and FIT and the TRIS/Na condition. After treatment with BIT and FIT little binding remained. However, BIT/FIT-treated sections incubated under KPO4/Na conditions demonstrated moderately high levels of specific binding which had an anatomical distribution markedly different from μ ([^{125}I]DAMGO) and δ ([^{125}I]deltorphin-II) receptors. Results for guinea pig brain. Using the Tris/Na condition and BIT/FIT-treated sections: [^{125}I]IOXY did not label μ or δ receptors and its binding was completely inhibited by 100 nM U69,593 or pretreatment with κ_1-selective site-directed acylating agent, UPHIT, indicating that this condition promotes labeling of κ_1 sites by [^{125}I]IOXY. BIT/FIT/UPHIT-treated sections incubated under KPO4/Na conditions demonstrated moderate levels of specific binding which had an anatomical distribution markedly different from μ ([^{125}I]DAMGO), δ ([^{125}I]deltorphin-II) or κ_1 receptors. Conclusions. Pretreatment with BIT and FIT eliminates [^{125}I]IOXY binding to μ and δ receptors. Using rat and guinea pig brain sections depleted of μ, δ and κ_1 sites, [^{125}I]IOXY labels opioid receptors with a novel anatomical distribution. We speculate that these may be subtypes of the κ_2 receptor.

EFFECTS OF LEVORPHANOL, BUPRENORPHINE AND BUTORPHANOL ALONE AND IN COMBINATION WITH MORPHINE IN A RAT TAIL WITHDRAWAL PROCEDURE

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The antinociceptive effects of morphine, levorphanol, buprenorphine and butorphanol were examined in Long-Evans rats in a rat tail-withdrawal procedure using 50 and 52° C water (50°W and 52°W). Morphine (1.0-30.0 mg/kg), levorphanol (0.1-1.0 mg/kg) and buprenorphine (0.03-3.0 mg/kg) produced dose-dependent increases in tail withdrawal latency (*i.e.,* increased percent antinociception) when tested with both temperatures. Butorphanol(0.3-56.0 mg/kg) produced increases in percent antinociception when examined at 50°W, and failed to produce appreciable levels of antinociception at the 52°W. The morphine dose-effect curves were then redetermined in combination with various doses of the other opioids. In the presence of levorphanol (0.1 or 0.3 mg/kg) or buprenorphine (0.03 or 0.3 mg/kg), the morphine dose-effect curves were dose-dependently shifted to the left and upward at both 50°W and 52°W. In the presence of increasing doses of butorphanol, there was a dosedependent enhancement of morphine at 50°W. At the same time (in the same animals) these doses of butorphanol produced a dose-dependent antagonism of morphine at 52°W. In all of these cases, the degree of leftward and upward shift observed could be predicted from the effects of the drug when given alone, and the degree of shift observed did not depend on the efficacy of the test opioid. Taken together, these results suggest that when a drug acts as an agonist alone, the dose-effect curve of another agonist will be shifted to the left or upward in an additive manner, and when a drug produces no effect alone, it can antagonize the effects of an agonist.

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CENTRAL AND PERIPHERAL INTERACTIONS OF MU AND DELTA OPIOID RECEPTORS

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In several standard models of analgesia, the antinociceptive effects of morphine are potentiated by subanalgesic doses of [D-Pen^2, D-Pen^5] enkephalin (DPDPE), leading to the expectation that mu-delta opioid combinations would provide more effective antinociception than mu opioids alone. This hypothesis is tenable only if mu opioid side effects, such as constipation, arc not potentiated by delta agonists in parallel with analgesia. Male ICR mice (20-25 g) were given i.c.v. or i.p. injections of morphine alone, DPDPE alone, or combinations of morphine and DPDPE in ratios based upon equieffective doses (D_{50} values) of each. Gastrointestinal transit was assessed by gavage with $Na_2{}^{51}CrO_4$ in saline from the distribution of ^{51}Cr in the stomach and intestine. Isobolographic analysis indicated superadditive interactions between morphine and DPDPE when both agonists were administered i.c.v. However, when morphine and DPDPE were given i.p., their effects were additive, not superadditive. Mu-delta opioid interactions in the periphery may differ from those in the CNS and peripherally administered mu-delta opioid combinations may enhance analgesia without concomitant exacerbation of constipation.

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RELEASE OF DYNORPHIN A FROM THE PREOPTIC ANTERIOR HYPOTHALAMUS AFTER ICV INJECTION OF NEUROTENSIN

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We have demonstrated that the k opioid receptor agonist dynorphin A1-17 (Dyn) induces hypothermia when it is given into the brain, suggesting a role for the k receptor in the central mediation of thermoregulation. Our results have also shown that ICV injection of neurotensin (NT) produces hypothermia as well and that NT in combination with the k-receptor agonist U50,488H has an additive hypothermic effect. Because both NT and Dyn and their receptors are co-localized in the preoptic anterior hypothalamus (POAH), a primary central site for body temperature (Tb) control, we investigated whether endogenous Dyn can be released from the POAH after ICV injection of NT by using microdialysis method. Artificial cerebrospinal fluid was infused at rate of 2 µl/min into the POAH of freely moving male S-D rats through a microdialysis probe. Samples were collected every 40 min for 4 hrs and analyzed for Dyn level by radioimmunoassay. Baseline release of Dyn in the POAH was 0.42 ± 0.16 fmol/40 min. ICV injection of NT (0.3-5 µg) produced dose-related hypothermia (-0.8 to -2.0 °C) and induced 150- 270 % increase in Dyn release over baseline during the 40- and 80-min postinjection periods. Pretreatments with a NT analog, [D-Trp^{11}]-NT (10 ng), which had no effect on Tb by itself, attenuated NT (5 µg)-induced hypothermia (maximum Tb response went from -2.0 to -0.8 °C) and reduced NT (5 µg)-induced elevation of Dyn level (from 270 % to 150 % during the 40-min collection period and from 160 % to 102 % during the 80-min collection period). Pretreatment with the k receptor antagonist nor-BNI (1 µg) also reduced NT (5 µg)-induced hypothermia (from -2 to -1.2 °C). These results indicate that endogenous Dyn in the POAH is involved in the hypothermic response of rats to ICV injection of NT.

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THE RELATIONSHIP BETWEEN µ AND κ OPIOID RECEPTORS IN BODY TEMPERATURE REGULATION

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Previous studies showed that icv injection of a κ opioid receptor agonist decreased body temperature in rats, and icv injection of a µ opioid receptor agonist increased body temperature. In conducting a dose-response study with the selective κ antagonist nor-BNI, we found that a low dose (1.25 nmol,icv) of the antagonist has no effect on body temperature and a high dose (25 nmol, icv) can increase body temperature. It was hypothesized that the reason for the body temperature increase induced by icv injection of nor-BNI is that it blocks the κ opioid receptor and releases its inhibition of µ opioid receptor activity. To determine whether the body temperature increase caused by nor-BNI was a p-receptor-mediated effect, we administered the selective µ antagonist CTAP (1.0 nmol,icv) 15 min after nor-BNI (25 nmol,icv, t=-30') and measured rectal body temperature for three hours using a digital thermometer in unrestrained rats. SD rats were used in the present study. Body temperature measurements and cannulae implantation into the lateral ventricle were carried out according to standard procedures in our laboratory. Statistical analysis of difference between groups was assessed with a two-way analysis of variance (ANOVA) followed by Duncan's test. $P<0.05$ was taken as the significant level of difference. The results showed that icv injection of CTAP (1.0 nmol,icv) can significantly block the body temperature increase induced by icv injection of 25 nmol of nor-BNI during the first 45 minutes of measurement ($p<0.05$). These results suggest that nor-BNI may block κ opioid receptors, allowing endogenous κ opioid receptor activity to be seen and points to a tonic balance between µ and κ opioid receptors.

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ROLE OF BRAIN OPIOIDS IN THE DEVELOPMENT AND MAINTENANCE OF HYPERTENSION IN RESPONSE TO STRESS

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Opioid peptides have been implicated in modulating autonomic function under basal and stressful conditions, but their role in regulating cardiovascular function remains unclear. The borderline hypertensive rat (BHR) is a unique and useful animal model of neurogenic hypertension because its genetic background makes it susceptible to the hypertensive effect of stress. In this study, we examined the effect of a time limited period of restraint stress in the development of hypertension and the role of brain opioids on the development and maintenance of hypertension in 8 week old BHR. We found that restraint stress, 2 hr daily, 5 days a week for 4 weeks, caused a significant rise in systolic blood pressure throughout the period of stress. Moreover, stressed BHR continued to have higher blood pressure compared to the control group 10 weeks after the end of stress. Intracerebroventricular (icv) administration of the mu-opioid receptor agonist DAMGO (5 nmole), produced a significant rise in BP (systolic 29.1±3.5; diastolic 11.5±5.4; mean 18.4±2.1 mmHg) and HR (60.8±9.8 bpm) 10 min after injection and continued to rise for 15-20 min before reaching a plateau. ICV administration of the delta opioid agonist DPDPE (50 nmole) or saline had no effect on BP or HR. Restraint stress in saline-treated rats evoked an increase in BP and HR. On the other hand, rats pretreated with DAMGO showed only a slight increase in BP with no change in HR due to stress applied 20 min after drug. DAMGO also produced a significant increase in plasma epinephrine (12.71±1.7 pmole/ml) and norepinephrine (16.32±1.9 pmole/ml). Restraint stress potentiated this increase in plasma catecholamines. These data support the involvement of mu receptors in the development and maintenance of hypertension due to stress.

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AGONIST AND ANTAGONIST EFFECTS OF METHOCLOCINNAMOX ON RESPIRATION IN RHESUS MONKEYS

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Clocinnamox is an insurmountable opioid antagonist. However, a clocinnamox derivative, methoclocinnamox (MC-CAM), exhibited both agonist and antagonist properties in analgesic assays (Woods *et al.* 1995). In this experiment we studied the extent and time course of the agonist effect (initial respiratory depression) of MC-CAM, and MC-CAM's antagonist effects upon morphine- or heroin-induced respiratory depression after MC-CAM treatment. Six adult rhesus monkeys were exposed to normal air and air mixed with 5% CO2; respiratory frequency (f), tidal volume (Vt) and minute volume (Ve) were measured using a pressure-displacement plethysmograph technique. All parameters of respiratory function were decreased after administration of MC-CAM (0.032 - 1.0 mg/kg, im), dose-dependently, and were antagonized by the opioid competitive antagonist, quadazocine. MC-CAM's agonist effects (1 mg/kg) lasted less than 24 h. Under control conditions, morphine and heroin, which were injected using a cumulative dosing procedure, depressed markedly the respiration in a dose-dependent manner. After treatment with MC-CAM (1 mg/kg), the dose-response curves of both morphine and heroin were quite shallow. The dose-response curves of morphine and heroin were restored to their control levels at 21 and 17 days, respectively. These results suggest that MC-CAM possessed opioid agonist and antagonist properties in an assay of respiratory depression and the antagonist effects of MC-CAM (1 mg/kg) persisted long after the disappearance of its agonist effects, lasting for longer than two weeks.

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EXAMINATION OF THE DISCRIMINATIVE-STIMULUS PROPERTIES OF BUTORPHANOL IN RATS

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The present study investigated the discriminative-stimulus effects of morphine or butorphanol and was designed to elucidate which opiate receptor subtype(s) mediate(s) these effects. Four rats were trained to discriminate 5.6 mg/kg morphine from saline. A second group of six rats was trained to discriminate 0.32 mg/kg butorphanol from saline. In morphine-trained rats, morphine, butorphanol and fentanyl completely substituted for morphine while *d*-amphetamine, and *d*-pentazocine did not. The stimulus effects of morphine and butorphanol were antagonized by naltrexone (.01, .1 or 1 mg/kg). Apparent pA_2 values (± standard error) for interactions between naltrexone and butorphanol or morphine were similar: 7.2 (± 0.99) and 7.3 (± 0.65), respectively. In butorphanol-trained rats, butorphanol, morphine and fentanyl fully substituted for butorphanol, while PCP, *d*-amphetamine, and *d*-pentazocine did not. Neither the selective kappa agonist, U50,488, nor ethylketocyclazocine (EKC) fully substituted for butorphanol, however EKC did produce partial substitution (68% butorphanol-appropriate responding). The stimulus effects of butorphanol, morphine, and fentanyl were antagonized by naltrexone (01, .1 or 1 mg/kg). Apparent pA2 values for interactions between naltrexone and butorphanol, morphine, or fentanyl were 7.7 (± 0.2), 7.5 (± 0.2), and 7.9 (± 0.1), respectively. The stimulus effects of morphine were antagonized by butorphanol (0.03 mg/kg) as evidenced by a rightward shift in the morphine dose-effect curve. Taken together, these data suggest that the discriminative-stimulus effects of butorphanol are mediated by mu receptors.

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MORPHINE DISCRIMINATION IN LABORATORY RATS: THE SIGNIFICANCE OF WEIGHT REDUCTION TO PERFORMANCE

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The purpose of this experiment was to investigate how weight reduction effects the performance of rats on a drug discrimination task in which morphine and saline serve as discriminative stimuli which signal the rat as to which bar to press in a two-lever operant conditioning paradigm. Ten naive male Long-Evans hooded rats, weighing between 441-531 gms at the start of the study, were tested at 80% and 90 % of their *ad lib.* weights. Half of the subjects were trained to bar press on the left (L) bar and half on the right (R) bar and were placed on a drug discrimination paradigm which required that they press their training bar when given an IP saline injection and the other bar when given 6 mg/kg morphine IP until they received 50 a reinforcements (RRLLRL pattern). An analysis of first responses demonstrated that when animals were tested at the 90% weights the mean correct first response was 63% while subjects tested at 80% weights chose the appropriate bar over 74% of the time. At the higher body weight, only 40% of the subjects achieved criterion performance while at the lower body weight, 80% of subjects achieved criterion performance. A closer analysis of the data indicated differences in the number of sessions it took the subjects to learn the discrimination. Results indicating that drug discrimination is sensitive to the weight of the animals may help us to understand the relationship between level of food deprivation and memory storage and retrieval processes under various drug conditions.

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SELECTIVITY OF NALTREXONE EFFECTS IN THE RHESUS MONKEY ON ORAL REINFORCERS: ETHANOL, SUCROSE, AND PHENCYCLIDINE

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In the observations reported herein, we have studied whether naltrexone will modify reinforced-responding of a variety of substances delivered orally to rhesus monkeys (N= 3-5). The monkeys were exposed to two concurrently available fluids. Water was always available as a comparison to one of the other substances studied. Each drug was studied at a concentration that maintained responding at rates above the vehicle control (water). Under these circumstances, naltrexone (0.032-0.32 mg/kg) was administered occasionally prior to a period where the monkeys responded to obtain drug and water under a concurrent fixed-ratio schedule of reinforcement. At doses of 0.1 and 0.32 mg/kg, naltrexone dose-dependently reduced both ethanol- and sucrose-reinforced responding by a comparable amount, but did not effect the concurrently available water. Naltrexone, at these doses, decreased phencyclidine-reinforced responding and the concurrently available water, but the effect was not systematic across the monkeys tested. Thus, naltrexone reduced the reinforcing effects of these oral substances differently. We are now examining whether other opioid antagonists will have similar patterns of effect on oral reinforcers.

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DISCRIMINATIVE STIMULUS EFFECTS OF DOPAMINERGIC COMPOUNDS IN BUTORPHANOL-TRAINED PIGEONS

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The purpose of the present experiment was to examine the influence of dopaminergic activity on the discriminative stimulus effects of butorphanol. In separate groups of pigeons trained to discriminate either 0.1 mg/kg (low) or 5.6 mg/kg (high) butorphanol from saline, (+)-amphetamine, a dopamine (DA) releaser and re-uptake inhibitor, engendered predominately saline-appropriate responding and failed to alter the butorphanol dose effect curves. In the low-dose group, the DA releasers, amantadine and amfonelic acid, substituted partially, and engendered predominately saline-appropriate-responding in the high-dose group. The D1 agonist, SKF-38393, and the D2 agonist, quinpirole, substituted partially in the low-dose group, and engendered predominately saline-appropriate responding in the high dose group. Cocaine and mazindol, both DA re-uptake inhibitors, substituted partially for the butorphanol stimulus in both training dose groups. Doses of cocaine that produced 45% and 63% drug-appropriate responding in the low-dose group, and 30% and 43% drug-appropriate responding in the high-dose group did not alter the butorphanol dose-effect curves; that is, these drugs interacted with butorphanol in a less than additive manner. Similarly, a dose of mazindol that produced 40% and 21% drug-appropriate responding in the low- and high-dose groups, respectively, did not alter either butorphanol dose-effect curve. Taken together, these results suggest that the stimulus effects of low training doses of butorphanol overlap with direct and indirect DA agonists, whereas the stimulus effects of high training doses of butorphanol overlap with DA re-uptake inhibitors. In addition, the manner in which these dopaminergic compounds interact with the butorphanol stimulus is less than predicted given the effects of these drugs when administered alone.

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INCREASED CEREBRAL ACTIVITY SIX DAYS AFTER MORPHINE TREATMENT, DRUG AND CONDITIONED EFFECTS

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To characterize the underlying neuroanatomical substrate responsible for the persistence of morphine sensitization, changes in the local cerebral metabolic rate for glucose ($LCMR_{glu}$) were examined in 95 brain regions of male F-344 rats, in the presence and absence of drug associated cues, using the 2-deoxy-D-[1-^{14}C] glucose method. Six days after the last of four, 10 mg/kg (sc) doses of morphine there were increases in basal metabolic activity. Although these changes were found to be more extensive in the presence of drug-associated cues, a basic underlying pharmacological effect of the morphine sensitization on basal brain activity was found in nonconditioned rats. These latter regions, in which a lasting pharmacological effect occurred, were found in forebrain areas including the shell of the nucleus accumbens and areas of the prefrontal cortex. Interestingly, the core of the nucleus accumbens and regions of the caudate were found to have an increased $LCMR_{glu}$ only in the presence of conditioned cues, indicating conditioned brain activity in limbic and motor areas without observable changes in behavior. The $LCMR_{glu}$ changes in the presence of cues may model changes associated with craving.

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EFFECTS OF CLOCINNAMOX IN COMBINATION WITH OPIOIDS IN A PRIMATE SHOCK-TITRATION PROCEDURE

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Effects of the irreversible, p-selective opioid antagonist clocinnamox (C-CAM) were assessed alone and in combination with morphine, buprenorphine, and U50-488 in squirrel monkeys responding under a shock-titration procedure. In this procedure, shock intensity increased every 15 s from .01 mA to 2.0 mA in 30 increments. Five lever presses during any given 15 s shock period produced a 15 s time-out after which shock resumed at the next lower intensity. When given alone, morphine, buprenorphine, and U50-488 dose-dependently increased the intensity below which the monkeys maintained shock 50% of the time (median shock level, MSL). When combined with morphine, C-CAM (0.01-0.1 mg/kg) produced dose-dependent rightward shifts in the morphine dose-effect curves for MSL as early as 4 hours after administration. Morphine failed to produce maximal effects on MSL in the presence of the largest dose of C-CAM (0.1 mg/kg). In contrast, buprenorphine failed to produce maximal effects in the presence of 0.03 mg/kg C-CAM. In addition, buprenorphine's effects returned to control values 17 days after administration of C-CAM whereas morphine's effects returned to control values by day 10. C-CAM did not alter U50-488's effects on MSL or response rate. These data suggest that morphine and buprenorphine increase MSL via activity at m-opioid receptors and that morphine produces these effects with higher intrinsic efficacy than does buprenorphine. Supported by NIDA grants DA00033, DA02749, and DA07244.

CHANGES IN SENSITIVITY TO THE RATE-DECREASING EFFECTS OF OPIOIDS IN PIGEONS TREATED CHRONICALLY WITH LAAM.

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One treatment for opioid dependence is chronic administration of the long-acting μ opioid l-α-acetylmethadol (LAAM). The purpose of this study was to examine the effects of daily exposure to LAAM in seven pigeons responding under a FR20 schedule of food presentation. LAAM (1.0-5.6 mg/kg/day) decreased sensitivity to morphine and increased sensitivity to naltrexone in a dose- and time-dependent manner with maximum shifts in the dose-effect curves of 6-fold right and 1000-fold left, respectively. LAAM also decreased sensitivity to etonitazene and fentanyl and increased sensitivity to nalorphine and nalbuphine; sensitivity to enadoline and ketamine was slightly increased during chronic LAAM treatment. Thus, chronic LAAM treatment confers cross-tolerance to morphine, etonitazene and fentanyl. When LAAM treatment was suspended for 24 hr, response rates decreased to 33% of control and this disruption was reversed by the acute administration of morphine. Increased sensitivity to naltrexone as well as disruptions in food-maintained responding upon termination of LAAM treatment indicate that dependence developed to LAAM under these conditions. Acute administration of LAAM can produce qualitatively similar changes in sensitivity to other drugs, although the magnitude of these effects is greater during chronic LAAM treatment. Tolerance and cross-tolerance to agonists as well as increased sensitivity to opioid antagonists can be similar during treatment with morphine or LAAM; however, sensitivity to the low efficacy opioid agonist nalbuphine is increased during chronic LAAM treatment and not during chronic morphine treatment, suggesting that dependence on LAAM is not identical to dependence on morphine. Moreover, the enhanced effects of other drugs under these conditions might predict the effects of these drugs in humans receiving LAAM. **ACKNOWLEDGEMENTS:** Supported by USPHS Grants DA05018 and DA05579.

ALTERATIONS OF HEROIN SELF-ADMINISTRATION AND μ-OPIOID BINDING BY INTRA-ACCUMBENS ß-FNA IN RATS

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ß-FNA has been shown to alkylate μ-opioid receptors both *in vivo* and *in vitro* and decreases heroin self-administration (Martin *et al.,* 1995). This study was undertaken to determine the effect of μ-opioid receptor alkylation in the nucleus accumbens (NAcc) on heroin self administration. Responding on a lever was engendered by infusions of 60 μg/kg of heroin. Once responding was stable, animals were administered 0, 0.05, 0.25, 1.25, or 2.5 nmol of ß-FNA bilaterally into either the rostra1 pole or caudal NAcc in 1 μ1 of artificial CSF (aCSF). Administration of aCSF was without effect, however both 0.25 and 1.25 nmol of ß-FNA increased the number of infusions by 750-80% when administered into the caudal NAcc. These doses had no significant effect when administered into the rostra1 pole. 2.5 nmol of ß-FNA significantly reduced the number of infusions when administered into the rostra1 pole, but significantly increased the number of infusions when administered into the caudal Nacc. Furthermore, greater increases were found over the first two weeks following administration of 2.5 nmol of ß-FNA into the caudal NAcc compared to lower doses. Autoradiographic analysis of [^{3}H]DAMGO binding demonstrated a 70% loss in μ-opioid binding that was confined to the NAcc following administration of 2.5 nmol of ß-FNA. The time course of the effect of ß-FNA on [^{3}H[DAMGO binding and DAMGO-stimulated G-protein activation is currently being assessed for comparison with the behavioral data. Therefore, decreasing μ-opioid receptor density in the rostra1 pole affects heroin self-administration differently than in the caudal NAcc. Supported by NIDA grants K21-DA-00247 and DAO-01999

MU-OPIOID AGONISTS POTENTIATE AMPHETAMINE-INDUCED CIRCLING IN THE NIGRALLY LESIONED RAT

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Dopamine release in the nigrostriatal tract is increased by stimulaton of mu-opioid receptors. We hypothesized the mu-opioid receptor agonists would potentiate amphetamine (AMPH)-induced turning in rats with this tract unlaterally lesioned with 6-hydoxydopamine. AMPH (1.0 mg/kg) was administered SC concurrently buprenorphine (0.01-1.0 mg/kg), fentanyl (0.01-0.056 mg/kg), levorphanol (0.1-1.0 mg/kg), meperidine (3.0-30 mg/kg), methadone (0.3-3.0 mg/kg), morphine (1.0-10 mg/kg) or dextrorphan (1.0-10 mg/kg), the optical isomer of levorphanol. Animals were placed into individual rotometers and then tethered to a direction-sensitive sensor. The number of complete ipsilateral turns every 15 min for 4 h was recorded by a computer. Buprenorphine, levorphanol, and methadone produced turning alone, while all of the drugs were found to potentiate AMPH-induced circling. To ensure that these effects were due to an opioid receptor, naltrexone (NTX) was administered prior to the two injections. NTX blocked only the effects of morphine. When NTX (0.1-10 mg/kg) was administered with AMPH alone, the antagonist was found to potentiate AMPH-induced circling. Activation of mu-opioid receptors does potentiate amphetamine-induced turning. However, this turning cannot always be blocked by naltrexone, due to its effects of amphetamine-induced turning. The role of individual opioid receptors in NTX potentiation of amphetamine-induced turning needs to be investigated further.

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CROSS TOLERANCE TO THE EFFECTS OF MU OPIOIDS: ROLE OF MAINTENANCE DOSE AND INTRINSIC EFFICACY

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The development of tolerance and cross tolerance to the rate-decreasing effects of several mu opioids were examined in rats receiving either 3.0 mg/kg/day or 30 mg/kg/day butorphanol. During the prechronic condition, butorphanol, buprenorphine, morphine, fentanyl and sufentanil each produced dose-related decreases in response rate. After rats received daily supplemental injections of butorphanol for approximately eight weeks, the dose-effect curves for butorphanol, buprenorphine, morphine and fentanyl were shifted rightward relative to those obtained during the prechronic condition. The extent to which these curves were shifted to the right differed across drugs, however, with greater shifts observed in the curves for butorphanol and buprenorphine than in the curves for morphine or fentanyl. Across drugs, shifts were greater in rats receiving 30 mg/kg/day butorphanol than in rats receiving 3.0 mg/kg/day butorphanol. The dose-effect curves for sufentanil were not altered during the chronic regimen. These data suggest that the development of tolerance and cross tolerance to the rate-decreasing effects of mu opioids is dependent upon such pharmacological variables as the maintenance dose of the toleragen and the intrinsic efficacy of the test compound.

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FLUOXETINE RAISES THE THRESHOLD FOR REWARDING BRAIN STIMULATION IN RATS.

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The effects of fluoxetine (FLX) on rewarding brain stimulation were determined in 8 Wistar rats using a rate-independent discrete-trial threshold measure. Rats were implanted with bipolar, stainless steel electrodes either into the ventral tegmental area (VTA) or medial forebrain bundle (MFB). Acute administration of FLX significantly raised the reward threshold (decreased sensitivity) at doses of 2.5, 5.0, 10.0 and 20.0 mg/kg, i.p., without altering latency of response. There was no significant variance as a function of electrode placement. In order to determine the effects of chronic treatment, daily injections of 5.0 mg/kg FLX were administered to rats for 21 days. Chronic treatment of FLX continued to significantly elevate rewarding thresholds with no evidence of tolerance. These results suggest that the antidepressant effects of FLX are not the result of excitation of brain reward systems.

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GAMMA-VINYL GABA RAISES BRAIN-STIMULATION REWARD THRESHOLDS

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Acute administration of gamma-vinyl GABA (GVG), an irreversible inhibitor of GABA transaminase, elevates levels of GABA in nerve terminals. An experiment by Chen et al. (1995) found that acute administration of GVG inhibits striatal dopamine (DA) release and attenuates the increases in extracellular striatal DA and locomotor activity induced by cocaine administration. In order to examine potential modulatory effects of GABA on DA-mediated reward, the effects of four doses of GVG (100,200,300 and 400 mg/kg) on thresholds for brain-stimulation reward (BSR) were determined in six male F-344 rats with bipolar electrodes implanted in the medial forebrain bundle. GVG raised BSR thresholds in a dose-dependent manner without significant effects on motor performance. These results suggest that elevated GABA levels may attenuate DA-mediated reward.

REFERENCE

Chen, C.E.; Straughter-Moore, R.M.; Tedeschi, D.L.; Russo, N.B.; Alexoff, D.L.; Volkow, N.D.; Fowler, J.S.; Chaurasia, C.S.; and Dewey, S.L. Pharmacologic modulation of cocaine-induced dopamine release and locomotor activity: a potential therapeutic strategy for cocaine abuse. Soc Neurosci Abstr Vol 21(3), p 1956

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EFFECTS OF CAFFEINE ON ACQUISITION AND MAINTENANCE OF I.V. NICOTINE SELF-ADMINISTRATION IN MONKEYS AND RATS

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Epidemiological reports indicate a correlation between coffee drinking and tobacco smoking and various behavioral observations indicate that these two licit drugs can interact additively. In the present experiments we investigated the effects of caffeine on the reinforcing properties of nicotine. Squirrel monkeys responded under fixed-ratio 30 schedules of either food delivery or i.v. nicotine injection with 4-min timeout periods after each injection or food delivery. Presession injection with caffeine (10-30 mg/kg i.m.) increased responding maintained by nicotine (0.01-0.03 mg/kg/inj) but not responding maintained by food. Larger doses of caffeine (56-100 mg/kg i.m.) disrupted behavior maintained by both nicotine and food. When timeout value was decreased from 4-min to 10-sec, responding was not maintained above saline levels by nicotine, but pretreatment with caffeine dramatically increased responding for nicotine. In Sprague-Dawley rats we used an acquisition paradigm in which they learned to self-administer nicotine over 14 days under a fixed-ratio 1 to 5 schedule of i.v. injection with 20-sec timeouts after each injection. Rats consuming caffeine (50mg/day) in their drinking water for seven days prior to the beginning and throughout behavioral testing acquired intravenous nicotine self-administration (0.03 mg/kg/inj) much faster during 2-hr daily sessions than did controls. Adding caffeine to water-drinking controls facilitated nicotine self-administration. These findings demonstrate that in two species caffeine can potentiate the reinforcing properties of nicotine under various experimental conditions.

DOPAMINE RECEPTOR INVOLVEMENT IN THE DISCRIMINATIVE STIMULUS EFFECTS OF CAFFEINE IN RATS

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Despite the widespread use of caffeine by humans, the mechanisms by which caffeine produces its stimulant effects remains unclear. In attempts to understand these mechanisms, the stimulus effects of caffeine have been widely studied in humans and animals. The present study examines the mechanisms underlying the discriminative stimulus effects of caffeine in rats trained to discriminate i.p. injections of saline from either 10.0 mg/kg or 56.0 mg/kg of caffeine in a discrete trial shock termination/avoidance procedure. Rats trained on 10.0 mg/kg of caffeine acquired the discrimination within an average of 90 sessions and rats trained on 56.0 mg/kg of caffeine acquired the discrimination within an average of 69 sessions. The D1 receptor agonist, SKF 81297, and the D2 receptor agonist, R(-)propylnorapomorphine (NPA), substituted partially in rats trained on 10.0 mg/kg of caffeine, but resulted in predominantly saline lever responding in rats trained on 56.0 mg/kg of caffeine. The D1 receptor antagonists, SCH 23390 and SCH 39166, and the D2 receptor antagonists, eticlopride and sulpiride, resulted in predominantly saline lever responding in both the low and high caffeine training dose groups. On the otherhand, both D1 and D2 antagonists antagonized completely the stimulus effects of the low training dose of caffeine, but in general did not alter the stimulus effects of the high training dose of caffeine. These results confirm previous reports that low and high doses of caffeine produce qualitatively different stimulus effects, perhaps due to the differential involvement of dopamine in mediating these effects. Furthermore, these results suggest that both D1 and D2 receptor activation are required to produce stimulus effects that mimic the low training dose of caffeine.

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SUBJECTIVE EFFECTS OF CAFFEINE IN FORMERLY COCAINE-DEPENDENT HUMANS

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Whether persons attempting to stop cocaine use should avoid caffeine (another stimulant) is unclear. In the present study, 11 formerly cocaine-dependent adults (mean recovery time 4.0 ± 3.8 years) and 11 adults with no history of alcohol/drug abuse or dependence matched to the former group on age and gender drank one cup of coffee (caffeine content 0, 50, or 100 mg) per hour for five hours (for a total of 0, 250, or 500 mg) each morning for three days in a double-blind, randomized procedure. They completed self-report scales before the first cup and 50 min after each cup. After this three-day sampling period, participants' rank ordering of the three serving doses was determined from a paired-choice questionnaire. Caffeine did not increase cocaine-like-effect or desire-for-cocaine ratings. Ratings of "jittery" ($p < .05$) and "anxious/tense/nervous" ($p < .10$) increased more with caffeine among the formerly cocaine-dependent participants. Ten experimental and nine control participants selected an active dose as their first choice, although neither group reported a significant preference between the two active doses. These results suggest that cocaine-dependent persons do not need to avoid caffeine although they have increased sensitivity to the anxiety and jitteriness associated with 3-5 cups of brewed caffeinated coffee relative to persons with no history of drug abuse/dependence

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ROLE OF PHYSICAL DEPENDENCE ON THE RELATIVE REINFORCING EFFECTS OF CAFFEINE AND PLACEBO

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The present study was undertaken to explore the role of caffeine physical dependence in caffeine reinforcement. Volunteers abstained from all dietary sources of caffeine for 32 consecutive days. All experimental administration of caffeine was oral via capsules under double-blind conditions. Volunteers were exposed to a chronic caffeine phase (150 mg/70 kg b.i.d.) for 12 days and a chronic placebo phase for 12 days with order of phases counterbalanced across subjects. On two days immediately following each phase, subjects received two challenge doses (caffeine, 150 mg/70 kg b.i.d. or placebo), also in counterbalanced order. In the afternoon of each challenge day, subjects 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 challenge drug again or receiving varying amounts of money, and a choice between the two challenge drugs (caffeine or placebo). This form also included negative amounts of money to assess how much subjects would forfeit from their pay to avoid aversive effects (*i.e.,* withdrawal symptoms after placebo). During a third day, one of the subject's previous choices on the Multiple-Choice Forms was randomly selected and the consequence of that choice was implemented. Placebo administration to volunteers maintained on chronic caffeine significantly produced typical caffeine withdrawal symptoms (*e.g.* fatigue, mood disturbance) relative to the other three challenge conditions. Volunteers receiving placebo in the chronic caffeine phase chose to forfeit more money ($2.35 average) than in the other three challenge conditions. Caffeine was chosen more frequently than placebo in the chronic caffeine phase than in the chronic placebo phase. These findings show that caffeine served as a reinforcer in volunteers who were physically dependent on caffeine (*i.e.* chronic caffeine condition) but not in those who were not physically dependent (*i.e.* chronic placebo condition).

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DIFFERENTIAL SENSITIVITY TO METHAMPHETAMINE PLASMA CONCENTRATION IN EXTENSIVE AND POOR CYP2D6 METABOLIZERS

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Methamphetamine (MAMP), a CNS stimulant drug, is p-hydroxylated by CYP2D6 to less active p-OH-MAMP. CYP2D6 mutations leave approximately 7% of Caucasians with no active enzyme (poor metabolizers, of PMs); others have active enzyme (extensive metabolizers, or EMs). On two separate occasions, eight EMs and three PMs ingested 10 mg MAMP Hcl orally, once during 1.8 g $NaHCO_3$ qid and once during placebo qid, and pharmacodynamic effects were measured at baseline and hourly eight times after drug, when blood samples were also drawn; 0-10 hr urine was also collected. Because MAMP fractional clearance by p-hydroxylation is small, we predicted similar MAMP concentrations and subjective effects in EMs and PMs, with urine alkalinization decreasing urine MAMP, increasing plasma MAMP, and increasing p OH-MAMP in both fluids. Although assays confirmed the presence of substantial quantities of p-OH-MAMP concentrations. Within- and between-subject concentration-response slopes were markedly different in EMs and PMs, under both placebo and alkalinized urine conditions, with PMs more sensitive to MAMP plasma concentration differences than EMs on several measures includine Cole/ARCI sedation-motor, stimulation-motor, and stimulation-euphoria scales, ARCI amphetamine and MBG scales, and a visual analogue scale of "good effects." As plasma kinetic differences between EMs and PMs cannot account for these subjective effects differences, the data suggest either that brain/plasma ratios of active compounds differ between EMs and PMs or else that PMs have a steeper brain concentration-response function.

GENDER DIFFERENCES IN THE METABOLISM OF COCAINE IN THE RAT

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Behavioral work has indicated that female rats are more sensitive to the acute and chronic stimulatory effects of cocaine (coc) and amphetamine. For amphetamine, gender differences in metabolism play at least a partial role in this effect. The purpose of the current study was to investigate gender differences in the metabolism of coc in the rat. Coc, Benzoylecgonine (BE) and Ecgonine Methyl Ester (EME) were assayed by GC/MS from brain and plasma of male and female rats 5-90 minutes after an i.p. injection of 15 mg/kg coc. No gender differences were found in coc levels in either brain or plasma, with peak levels occurring 15 minutes after injection. In contrast, there were gender differences in the coc metabolic pathway. BE was the preferred metabolite in males, achieving levels 2-3 times higher than females in plasma (ANOVA $p < .01$ for gender). In contrast, EME formation was more prevalent in females, with levels 3-4 times higher than males in plasma and brain (ANOVA $p < .001$ for gender). In conclusion, while the metabolic pathways for cocaine appear to be different in male and female rats, comparable coc levels are achieved in both brain and plasma. These findings imply that the gender differences in the psychopharmacological response to cocaine are not dependent on metabolism, but rather reflect differences in sensitivity to the drug.

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GENDER DIFFERENCES TO THE TOXICITY BUT NOT THE STEREOTYPY PRODUCED BY AN ANALOG OF COCAINE

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The cocaine analog 3ß-(4-iodophenyl)tropan-2ß-carboxylic acid methyl ester (RTI-55) has been previously shown to bind to both dopamine and serotonin transporters with high affinity. While the binding parameters of this compound have been investigated, the behavioral effects have not. Previously RTI-55 had been observed to produce a long-lasting locomotor activation in mice. Work from this laboratory has demonstrated that RTI-55 generalizes to the cocaine discriminative stimulus in rats trained to discriminate 10 mg/kg cocaine from saline. We have also investigated the stereotypy produced by high doses of RTI-55 in male and female HS mice. This heterogeneously bred line was chosen to eliminate strain differences that may be present. Administration of a single dose of RTI-55 (0.5 - 20 mg/kg) produced an array of behaviors progressing from compulsive paw-licking to self-injurious behavior (SIB). Death occurred several hours to days following administration of RTI-55, preliminary data suggests that death may have been due to circulatory collapse. While there seemed to be no gender difference in the SIB observed, there was a striking gender difference in the mortality rate following RTI-55 administration. The calculated LD_{50} (and 95% confidence range) for males was 3.47 (2.12 - 5.68) mg/kg whereas the calculated values for female mice was significantly higher 7.57 (5.20 - 11.03) mg/kg (p 0.05). Prior administration of either the D1 antagonist SCH-23390 and the NMDA antagonist MK-801 attenuated lethality and SIB. Future studies are set to explore a possible basis for the gender difference in lethality and the neurochemical basis of SIB.

EFFECTS OF BUTYRYLCHOLINESTERASE AND CYMSERINE PRETREATMENT ON COCAINE-INDUCED MOTOR ACTIVITY

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Plasma butyrylcholinesterase (BChE) is the major cocaine-metabolizing enzyme in humans. Preliminary *in vitro* experiments have shown that the addition of horse-serum (HS) BChE to squirrel monkey plasma can accelerate the metabolism of cocaine. Therefore, we tested whether (HS) BChE or the selective BChE inhibitor cymserine could modify cocaine-induced locomotor activity in male Sprague-Dawley rats surgically prepared with jugular catheters. Three to five days later, three groups of rats were given either saline or HS-BChE (5,000 units) i.v. or cymserine (10.0 mg/kg) i.p. Locomotor activity was then monitored for 30 min. Half the rats in each group were then given an i.v. injection of saline and half were given iv. cocaine (1.0 mg/kg), and activity was monitored for an additional 120 min. Cymserine suppressed activity during the 30-min habituation period, but this suppression was not evident 30 min after injection. HS-BChE had no affect on activity during this period. Cocaine produced a clear increase in both distance traveled (DT) and stereotypy time (ST). Both HS-BChE and cymserine decreased cocaine-induced ST during the first 30 min following the cocaine injection, with HS-BChE also tending to decrease ST during the last 30 min. Cymserine potentiated cocaine's effect on both DT and ST 30-60 min following the cocaine. These preliminary results indicate that modulation of BChE activity might influence cocaine-induced motor activity. However, as these effects were small and restricted to the first hour after administration, further experimentation will be necessary to confirm these effects and determine the optimum dose, route of administration, and timing for BChE administration.

CORTICOSTERONE AND COCAINE INDUCED LOCOMOTOR HYPERACTIVITY

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The psychomotor effect of cocaine is thought to be related to cocaine's reinforcing properties, and locomotor response to a novel environment has been shown to be a predictor of vulnerability to drugs of abuse. The present studies examined the relationship between circulating corticosterone and the psychomotor response to cocaine in rats. Methods: Male Fisher rats were allowed to acclimate to the home cage environment for 1 week prior to the onset of experiments. In the first experiment, animals received saline in a binge pattern for 1, 3, 4, 5, or 14 days. In the second experiment, animals received 14 days of BPCA or saline and spontaneous locomotor activity was monitored in the home cage (see abstract of Ho et al, 1996). In the third experiment animals received 14 days of saline or BPCA or 13 days of saline followed by a single day of BPCA.. All animals were sacrificed 30 min following the last injection. Results: On the third day of saline injections, circulating corticosterone was significantly increased ($p<0.002$). Corticosterone returned to basal levels on the 4th day in the saline group and was at basal levels after 14 days of saline injections. Corticosterone levels were significantly elevated by 1 ($p<0.05$) or 2 ($p<0.01$) days of BPCA following 5 days of saline, or 14 days of BPCA ($p<0.001$). BPCA significantly increased spontaneous locomotor activity from Day 1 though 14, with no significant increase in locomotor activity in the saline control group, even on days shown to have elevated corticosterone levels. In a separate experiment, stress minimization by 13 days of saline injections did not attenuate the locomotor response to a single day of BPCA. Conclusion: Elevated circulating corticosterone may be associated with but is not sufficient to produce a locomotor effect following cocaine. Support: NIDA Center grant P50-DA05130, DA00049 to MJK; C.H. Li Award to YZ

d-AMPHETAMINE INCREASES HUMAN MOTOR ACTIVITY IN A RECREATIONAL ENVIRONMENT

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Individual differences in novelty- and amphetamine-induced motor activity are associated with psychostimulant reinforcement in animals. This study investigated spontaneous motor activity in humans as a potential marker for vulnerability to drug abuse. We hypothesized that (1) motor activity levels in a recreational environment would exhibit within-session (on task > off task) and between-session changes (novelty > repeated exposure); (2) *d*-amphetamine would dose-dependently and selectively increases motor activity; and (3) individual differences in environmental novelty- and *d*-amphetamine activity response would be positively correlated. Methods. Activity data were recorded from 12 nondrug abusing participants in a two-choice (placebo vs. 75 mg tripelennamine) oral, double-blind drug discrimination protocol. Before each 4-hr session, actometers were attached to the volunteer's dominant wrist and ankle. During each session, the volunteer remained in a recreational setting and could choose freely among various activities (computer games, billiards, reading, watching TV, listening to stereo headphones). At 1, 2, 3 and 4 hrs post-drug the volunteer completed subjective effect ratings. Reaction to novelty was measured upon initial exposure to the recreational setting (placebo). During the test phase, training drugs plus diazepam (2.5 and 5 mg) and *d*-amphetamine (5 and 10 mg) were administered in randomized, counterbalanced order. Raw data were cumulated from 20-sec bins to 10-min bins for statistical analyses. Results. As predicted, motor activity exhibited both significant within-session (on task > off task) and between-session changes (novelty > repeated exposure). *d*-Amphetamine dose-dependently and significantly increased wrist motor activity; a similar, nonsignificant trend was evident for the ankle site. The other drugs did not significantly change activity levels. Similar to previous animal studies, subjects with greater initial reactivity to the recreational setting generally showed greater activity response to *d*amphetamine, These results indicate that motor activity levels may serve as a useful measure of environmental and psychostimulant sensitivity.

WITHDRAWAL FROM CHRONIC BINGE PATTERN COCAINE IN THE FISCHER RAT: THE ROLE OF EXPECTANCY AND CONDITIONING

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Chronic binge pattern cocaine administration (BPCA) has been shown to produce behavioral sensitization in rats (Unterwald *et al,* 1994). This study addressed two related phenomena of classical conditioning: expectancy at the time when cocaine had been given and conditioning to the injection procedure. Method: Parallel studies of BPCA were conducted in two rooms: in each, six male rats received three daily injections of cocaine (15/mg/kg ip) in the morning for two weeks, and six received saline on the same schedule. After two weeks, rats in one room were left undisturbed. In the other room, three daily injections of saline were given to all rats. Spontaneous locomotor activity of each rat in its home cage was examined across 5 hr. Results: On the 13th day of BPCA, cocaine groups showed higher levels of spontaneous locomotor activity than did saline controls, $F(1,20)=11.35$, $p<0.005$, as in our earlier study, with no difference between like treatment groups in different rooms. On Withdrawal Day 1, rats in both cocaine groups showed significantly greater activity than did saline controls, $F(1,20)=9.28$, $p<0.01$, an effect of expectancy. By Withdrawal Day 3, when there was no significant difference between unhandled cocaine and saline treated rats, those given saline injections during cocaine withdrawal showed higher levels of activity than did the undisturbed cocaine withdrawal group, Newman-Keuls post hoc test $p<0.01$, an effect of conditioning to the injection. By Withdrawal Day 10, corticosterone levels in the injected cocaine withdrawal group were significantly lower than in the undisturbed group, Mann Whitney $U=5.0$, $p<.05$. Conclusion: Two distinct types of conditioning may account for both increased locomotor activity, and lower corticosterone, in rats given saline injections compared to those left undisturbed during withdrawal from chronic cocaine. These effects may be relevant to the human problem of relapse. Supported by NIDA Center Grant P50-DA05130; DA00049 to MJK; CH Li Award to YZ.

COMPARISON OF THE EFFECTS OF COCAINE AND FLECAINIDE ON CARDIOVASCULAR FUNCTION IN ANESTHETIZED RABBITS

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In addition to its indirect sympathomimetic actions, cocaine is a potent sodium channel blocker, arrhythmogenic and respiratory depressor agent. Other investigators have suggested that sudden death following cocaine is pro-arrhythmic in nature, occurring under similar circumstances as that due to specific anti-arrhythmic drugs, like flecainide. In this study, we investigated the effects of cocaine in anesthetized rabbits and compared them to equimolar or higher doses of flecainide. New Zealand White rabbits (2.5-3.5 kg, n=6/group) were anesthetized and prepared with arterial and venous catheters. Cocaine (0.3 or 2.0 mg/kg) or flecainide (2.4 or 5.6 mg/kg) were injected i.v. and cardiovascular and respiratory parameters were monitored. Cocaine produced clear dose-dependent decreases in mean arterial blood pressure and heart rate, a clear prolongation of the QRS interval and increases in respiratory rate. A dose of flecainide (2.8 mg/kg) that was equimolar to the 2.0 mg/kg dose of cocaine produced similar, but smaller effects on the QRS-complex and respiratory rate Flecainide had no effect on hemodynamics, even after doubling the dose to 5.6 mg/kg. These results suggest that in anesthetized animals, the cardiovascular effects of cocaine are more depressive to both hemodynamic and cardiac conduction than flecainide, and that the depressive effects on cardiac conduction and respiratory rate are primarily due to the local anesthetic action of cocaine.

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SEROTONIN-4 ANTAGONISTS (GR113808A AND GR125487D) REVERSES COCAINE INDUCED CARDIAC ARRHYTHMIA

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Cocaine abuse and dependence continues to be a growing public health problem worldwide. Acute cocaine intoxication is associated with a variety of cardiovascular abnormalities including sinus tachycardia, ventricular tachycardia and fibrillation, ventricular premature contraction and asystole. Recently it's been reported that activation of human arterial 5HT4 receptor is arrhythmogenic and may be involved in the genesis of atria1 fibrillation. In preanesthetized tracheotomized rats (400-450 grams), whose femoral vein and artery were canulated for the measurement of pulse rate, mean arterial pressure and the introduction of cocaine and 5HT4 antagonists, we examined the ability of 5HT4 antagonists (GR113808A, GR125487D) to reverse cocaine induced arrhythmias. These animals were attached to a mechanical respirator and breathed with room air (5 ml/kg, 48 strokes/min.). A limb lead II electrocardiogram was recorded on a micrograph jet recorder. Temperature was maintained at 37°C using a heating pad. 2 mg/kg of 5HT4 antagonists in saline was infused 30 min prior to cocaine infusion. Data on mean arterial pressure, pulse pressure and cardiovascular parameters were obtained two minutes after infusion of cocaine. Our results show a dose-dependent reversal of cocaineinduced arrhythmia without any significant alteration in baseline cardiovascular (QRS, PR intervals) parameters. Pretreatment with 2mg/kg of GR113808A or GR125487D increased the amount of cocaine required to induce sustained ventricular arrhythmia by 168±40% and 286±18% respectively. Post-treatment after sustained arrhythmia returned the animals to sinus tachycardia in 26±12 and 15±8 minutes respectively. The clinical implication is clear: these compounds may be useful in the emergency reversal of cocaine cardiotoxicity.

COCAINE'S (COC) EFFECT ON BRADYCARDIA INDUCED BY VAGUS NERVE STIMULATION IN CATS

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Recent data suggest that iv coc, 1 mg/kg, reduces vagal influence on the heart by blocking muscarinic receptors (Circulation 82: 939, 1993). To test this hypothesis directly, the effects of coc on bradycardia induced by stimulation of the vagus nerve were assessed in anesthetized (alpha-chloralose) cats pretreated with propranolol (1 mg/kg). Bradycardia was induced by electrical stimulation of the distal end of the right cervical vagus nerve with frequency set in each cat to elicit a heart rate (HR) response that was 50% of the maximal response attainable (1-4 Hz applied for 15 sec). These stimulation parameters decreased HR by -61±12 beats/mm (from 167±20 beats/min, n=6). Cumulative doses of coc were administered iv and the vagus nerve was again stimulated at 1 min and then at 6 min intervals after each dose. At least 30 min elapsed between coc injections. At no time did coc block the bradycardia elicited by vagal stimulation: 1 min after injection of the 0.25, 1.0 and 2.0 mg/kg doses, HR decreased by -68±14, -63±9 and -57±10 beats/min with stimulation, respectively. Coc did not affect baseline hr. In a separate group of cats (n=4), coc (4 mg/kg) did attenuate ($p<0.05$) the stimulation-induced bradycardia: hr decreased by -62±12 beats/min before and by -21±6 beats/min 1 min after coc. We conclude that coc in the 0.25-2.0 mg/kg dose range does not block muscarinic receptors that mediate vagal-induced bradycardia. The 4 mg/kg dose of the drug does reduce parasympathetic tone to the heart but the mechanism of this effect remains unknown.

CHANGES IN PHYSIOLOGICAL PARAMETERS OF RECENTLY ABSTINENT HOSPITALIZED COCAINE ADDICTS

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Physiological parameters of seven long term cocaine addicts were examined across the first five weeks of abstinence. Subjects were six male and one female HIV - 1 seronegative individuals meeting DSM-IIIR criteria for cocaine dependence. The mean age of the subjects was 28.6 + 2.0 years. The average duration of cocaine use was 3.8 years. Five patients used cocaine daily. All patients used cocaine by smoking route; one subject also used intranasally. Five of the seven subjects had used cocaine within the 24 hours prior to admission. Methods: Patients received no medication on days 1 - 7, placebo on days 8 - 21, and fluoxetine (20 mg) on days 22 - 35. ECGs taken at admission were compared to ECGs taken one week prior to admission. The subject's vital signs were taken daily. Body weight was measured each morning and caloric intake was calculated based on the amount of food consumed. Results: Patients' vital signs were: mean heart rate = 66.5 beats/min, mean blood pressure = 110/64 and did not change over the study period. ECGs of all seven patients were qualitatively within normal limits. Although the increase in caloric intake failed to reach statistical significance ($F(1,4) = 2.19$, $p<.08$.), it reached a maximum of 3900 kcal and remained constant. Mean body weight significantly increased during the first 21 days, $F(1,6) = 27.42$, $p<.001$, and then plateaued. Discussion: Resting vital signs of long term cocaine users do not differ from the normal population and are not altered by the administration of fluoxetine. Patients showed a period of "refeeding" during the first three weeks of study characterized by increased caloric intake and body weight.

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FAILURE TO DETECT COCAINE-INDUCED CONTEXT-SPECIFIC SENSITIZATION IN HUMAN COCAINE ADDICTS

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Our previous study, which utilized a two-day cocaine administration paradigm, failed to demonstrate cocainc-induced context-specific sensitization in human cocaine addicts (Pharm. Biochem. Behav., 49(3):583-588). In the current study, subjects participated in twice-daily drug administration sessions for four consecutive days. In one daily session subjects self-administered 96 mg cocaine (intranasally) and placebo powder in the other daily session. Distinct contextual environments (the nurse, room lighting, music, odor and taste) were paired with cocaine and placebo for the first four days. On the fifth day, one group 1 was "switched' and received cocaine under the placebo environment and placebo under the cocaine environment. Group 2 was unswitched. End-points included cardiovascular parameters and subjective effects. The absence of a significant effect of cocaine in the group 2 precluded detection of context-specific sensitization. Analysis of the data of days 1-4 of group 1 demonstrated statistically significant effects of cocaine vs. placebo, but no evidence of sensitization. The major conclusions of this study are: 1) Non-context-dependent sensitization does not occur under these experimental conditions. 2) The cardiovascular and subjective effects of 96 mg intranasal cocaine was much less than reported in the literature. This may be related to the drug use history of the subjects recruited for this study and suggests that tolerance to the cardiovascular effects of cocaine develops with heavy use. 3) The failure to observe, in two separate studies, cocaine-induced sensitization in humans raises questions about the relevance of this model to the study and treatment of cocaine addiction.

OLFACTORY EVOKED POTENTIAL DEFICITS IN ABSTINENT COCAINE ABUSERS

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Olfactory evoked potentials were elicited by odorous and nonodorous stimuli in 50 adults subjects: 26, subjects with histories of either cocaine (n=19) or alcohol (n=7) dependence, ten with histories of nicotine but no other drug dependence, two with clinical asnomia of peripheral origin, and 12 subjects without drug or olfactory disorders. The presentation of nonodorous stimuli (*i.e.,* a nasal air puff) did not elicit OEP component amplitude and latency differences among the groups. However, the presentation of odorous stimuli elicited a significantly (Group X Condition: $F=3,88$, $p<0.01$) smaller P1 component in the cocaine-dependent and anosmic groups than in the normal control and nicotine dependent groups. The P1 amplitude deficit in the cocaine-dependent group is consistent with case report data associating cocaine use with lesions of the peripheral and/or central olfactory apparatus.

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EFFECTS OF EQUITY AND *d*-AMPHETAMINE ON HUMAN COOPERATIVE RESPONDING

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In this study, the interacting effects of *d*-amphetamine and inequitable point distribution, a significant social variable, on cooperative responding were examined. Eight healthy male subjects between the ages of 18-40 were administered acute doses of placebo, 5 mg/70 kg, 10 mg/70 kg and 20 mg/70 kg *d*-amphetamine, thirty (30) minutes after an initial pre-trial. Each subject participated in multiple fifteen-minute trials Monday-Friday. Subjects were instructed that points exchangeable for money could be earned by working independently or with another person. Two schedule components repeatedly alternated during a trial. During the first, alone, component, subjects earned points exchangeable for money for themselves by pressing button "A." During the second, choice, component, subjects could earn points by working with the other person (button "C" presses) or independently (button "A" presses). Both options were concurrently available and points accumulated on counters marked "Your Earnings" and "Other's Earnings" or just "Your Earnings," respectively. Acute administration of *d*-amphetamine appeared to increase time allocated to the cooperative alternative when point distribution favored the subject and when the distribution of points exchangeable for money favored the fictitious other person only in subjects who did not have a history of stimulant use. The data suggests that drug history is significant in mediating the effects of drugs on human cooperative behavior.

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SELF-ADMINISTRATION OF COCAINE IN HUMANS, A PILOT STUDY

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Cocaine has high abuse potential primarily due to its strong reinforcing properties. Cocaine reinforced self-administration behavior could be changed with pharmacological and environmental factors in animals but its generalization to humans needs further testing. We conducted a pilot study to establish a paradigm in which a concurrent choice between repeated cocaine doses and money was used to determine the propensity of individuals to choose between cocaine and alternate reinforcers. Four male volunteers with a history of more than 2 gm/wk cocaine use were randomized to receive sample drug A (cocaine 25 mg) or drug B (placebo) intranasally every 30 minutes up to five times on two separate days. All subjects identified drug A as cocaine. On day three and four the subjects were offered a choice between drug A (cocaine 25 mg) and money ($0.75, $1.50, $3.00, $6.00 and $12.00) in a random order. Results show that after the sample doses of 25 mg of cocaine and placebo all four subjects recognized cocaine dose as active and chose to proceed with the study. Two subjects had a moderate high, one had mild high, and one subject did not have any effect on active cocaine sample day. During the choice days two subjects chose cocaine against $0.75 and $1.50, and money at $3.00 to $12.00 in both choice sessions. The third subject chose cocaine against $0.75, $1.50 and $3.00 consistently in both sessions before switching to money. The fourth subject chose money all five times during these sessions. Since self-administration of cocaine may be altered by other reinforcers in humans, this paradigm may be used for the development of new pharmacotherapies which may reduce self administration potential of cocaine.

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EFFECTS OF DELIVERY RATE AND NONCONTINGENT INFUSION ON COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS

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Seven male rhesus monkeys self-administered cocaine iv on an FR-30 schedule (TO 5 min) in the home cage during 1-hr sessions. With unit dose (.056 mg/kg/infusion for one monkey & .032 mg/kg/infusion for the rest) and infusion volume (.5 ml) held constant, the rate of delivery was manipulated (.125, .1875, .375, .75, & 3 ml/min). Reinforcement and response rates increased monotonically as a function of delivery rate, suggesting that delivery rate influences cocaine's reinforcing properties. Responding for the slowest infusion (.125 ml/min) was about the same as for saline. The effects of infusing cocaine noncontingently at this nonreinforcing rate were then examined. Noncontingent infusion (.125 ml/min) started 30 min prior to the self-administration sessions and continued throughout each session. The delivery rate of the self-administered infusion was manipulated as before. This treatment tended to flatten the effect curves. While two monkeys ceased responding when cocaine was given noncontingently, delivery-rate effect curves were clearly shifted upwards for two other monkeys. Most monkeys showed increases at the slower delivery rates. Noncontingent cocaine tended to decrease response and reinforcement rates in four monkeys that worked for food on a similar FR-30 schedule. In five other monkeys, plasma levels of cocaine were compared over time (1-60 min) following 5 ml infusions of cocaine (.32 mg/kg) at the .125 and 3 ml/mm delivery rates. The faster infusion produced a higher peak, but levels were equivalent after 5-7 minutes.

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COCAINE IV SELF-ADMINISTRATION IN C57BL/6J, A/J AND DBA/2J INBRED MOUSE STRAINS.

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Accumulating evidence suggests that there is a genetic predisposition to abuse drugs. The present experiments tested the hypothesis that the reinforcing effects of cocaine are influenced by genotype. For this purpose C57BL/6J, A/J and DBA/2J inbred mice were used as subjects and compared in the acquisition and maintenance of cocaine IV self-administration. All strains were initially trained to press a lever, then stabilized under a fixed ratio 2 (FR2) schedule for sweetened condensed milk as a reinforcer; subsequently, each subject was implanted with a permanent indwelling jugular catheter. Two days after surgery, mice began training under FR1 schedule, with cocaine 2.0 mg/kg/infusion as reinforcer, until acquisition criteria (75% of active lever pressings and at least 16/20 injections within 3 h for three consecutive days) was obtained. In 90 min session with unlimited reinforcers available, subjects were considered ready for dose-effect testing with the same stability criteria. Each dose of cocaine (0.5, 1.0, 2.0 and 4.0 mg/kg) was tested separately, during three consecutive days, and the dependent variable used was the number of reinforcers per hour, which expresses the rate of cocaine taking. On average, four days were necessary for A/J and DBA/2J mice to meet IV cocaine self-administration acquisition criteria, while four days were necessary for C57BL/6J mice. The dose-response curves for A/J and DBA/2J mice were significantly downward shifted when compared to the one for C57BL/6J mice ($F(2,5)=8.08$; $p<0.05$). These results suggest that A/J and DBA/2J mice are more sensitive to the reinforcing effects of cocaine, and that genetic differences underlie the maintenance of cocaine self-administration.

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EFFECTS OF KETOCONAZOLE ON INTRAVENOUS COCAINE SELF-ADMINISTRATION IN RATS

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Previous research from our laboratory has suggested tbe potential involvement of the hypothalamic-pituitary-adrenal (HPA) axis in cocaine reinforcement. In particular, we found that exposure to non-contingent electric footshock facilitated the acquisition of intravenous cocaine self-administration in rats. In another series of experiments, we demonstrated that surgical and pharmacological adrenalectomies abolished the acquisition and attenuated the maintenance of cocaine self-administration. Ketoconazole is an oral antimycotic used in the treatment of fungal disease which also blocks the synthesis of adrenocorticosteroids and functions as a glucocorticoid receptor antagonist. These experiments were designed to determine the effects of ketoconazole in adult male Wistar rats trained to respond under a multiple, alternating schedule of food reinforcement and cocaine self-administration. During daily 2-hr sessions, the rats were allowed access to food presentation (delivered under a fixed-ratio 10 schedule) and cocaine self-administration (fixed-ratio 4) during alternating 15 min periods. Prior to testing with ketoconazole, the rats were exposed to multiple cocaine extinction (saline) probes. Pretreatment with ketoconazole (0-25 mg/kg, ip), 30 minutes before the start of the behavioral session, did not affect food-maintained responding. However, cocaine self-administration was indistinguishable from saline extinction following ketoconazole administration, suggesting that these effects were specific for cocaine reinforcement. These data further underscore the potential role for corticosterone in cocaine reinforcement.

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ESTABLISHING ORAL COCAINE PREFERENCE WITHOUT AN ASSOCIATIVE HISTORY WITH A REINFORCER

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A stable, oral, schedule-induced polydipsic preference for cocaine solution to water can be instituted when cocaine is associated with an alcohol or glucose-saccharin vehicle and the vehicle solutes are gradually faded out. The present study investigated whether a cocaine preference also could be established by the avoidance of a concentrated lidocaine solution, rather than by an associative history with a special vehicle. Animals (N= 19) were exposed to daily 3-h polydipsia sessions for either 0.24 mg/ml cocaine or 0.19 mg/ml lidocaine for 33 sessions. When both drug solutions were concurrently presented (12 sessions), animals had no differential preference. By subsequently increasing cocaine and lidocaine concentrations to 0.48 and 2 mg/ml, respectively, cocaine solution was exclusively preferred to lidocaine, with a mean oral cocaine dose of 43.7 mg/kg. Cocaine preference (90%) persisted while lidocaine concentration was progressively decreased, and after it had reached zero (water). Thus, cocaine preference to water can be produced not only by an historical association of cocaine with a highly acceptable vehicle, but also by a history of avoiding a nonpreferred alternative solution. Using the same animals, lidocaine preference was determined by fixing lidocaine concentration at 0.38 mg/ml while subsequently increasing cocaine concentration from 0.48 to 2.5 mg/ml. However, preference for lidocaine solustion did not occur. Instead, oral cocaine preference persisted up to and including the highest cocaine concentration, 2.5 mg/ml. It is unlikely that a gustatory preference played a role in this choice, since animals initially did not prefer even a 0.24 mg/ml cocaine concentration. These results suggest that, under schedule-induction conditions, the avoidance of lidocaine solution forces the discrimination of the relation between high cocaine intake and its reinforcing effects, thus accounting for the institution of the observed cocaine preference.

PREFERENCE FOR ORAL LIDOCAINE TO COCAINE ESTABLISHED BY HISTORIC ASSOCIATION WITH A PREFERRED VEHICLE

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In daily, 3-h, oral schedule-induction polydipsic sessions, rats (N=16) preferred 0.19 mg/ml lidocaine (LIDO) to water after LIDO was first presented in a vehicle of 1.5% glucose + 0.08% saccharin, and the vehicle concentration was gradually reduced to zero. Then, half the animals (COC GRP) were rapidly faded to an isomolar 0.24 mg/ml cocaine (COC) in place of LIDO to determine if the preference would transfer to COC. The remaining rats (LIDO GRP) continued with the LIDO versus water choice. Mean percent drug preferences were: LIDO GRP 95% and COC GRP 83%. On subsequently presenting both groups with a LIDO versus COC choice, most rats preferred LIDO, and none preferred COC. LIDO preference strength was tested by slowly increasing its concentration to 0.54 mg/ml, while COC remained at 0.24 mg/ml. Preference for LIDO remained strong for LIDO GRP (870/o), while it declined for COC GRP (66%). In a parallel, unpublished study, COC preference was established by a similar vehicle-association history, but the present results indicate that even LIDO, a nonabused substance with similar gustatory properties, also can be preferred. Thus, inferences concerning oral preference for a substance known by other procedures (e.g., IV) to have reinforcing potential cannot be assumed to have a pharmacological basis in the absence of a proper negative control substance.

DISCRIMINATIVE STIMULUS EFFECTS OF *d*-AMPHETAMINE, BUPROPION, METHYLPHENIDATE AND TRIAZOLAM IN *d*-AMPHETAMINE-TRAINED HUMANS

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The discriminative-stimulus effects of *d*-amphetamine (*d*-AM), bupropion (BUP), methylphenidate (MTH) and triazolam (TRZ) were assessed in seven healthy, paid volunteers trained to discriminate between 20 mg *d*-AM and placebo. The study was conducted in three phases. During the sampling phase, 20 mg *d*-AM, identified by letter code (*e.g.,* Drug A), was administered one time and subjects were instructed to attend to the drug effects because in subsequent sessions they could earn money by correctly identifying when they had received Drug A. During the second sampling session, no capsules were administered and subjects were instructed to attend to the absence of the effects of Drug A because in subsequent sessions they could earn money by correctly identifying when they had not received Drug A. Drug-discrimination performance was assessed using a fixed-interval schedule of point presentation and point-distribution task. Points earned on the correct option ("Drug A" or "Not Drug A") were redeemable for money. Subject-rated drug effects were assessed concurrently. In a test-of-acquisition phase, *d*-AM was not identified and subjects reported their drug identification 1,2,3 and 4 hours after drug administration. Five of seven subjects were able to acquire and maintain the discrimination between 20 mg *d*-AM and placebo. These five subjects completed a test-of-novel-doses-and-drugs phase in which *d*-AM (2.5, 5, 10 and 20 mg), BUP (50, 100, 200 and 400 mg), MTH (5, 10, 20 and 40 mg) and TRZ (0.063, 0.125, 0.25 and 0.5 mg) were tested, and subjects were paid independent of their drug identifications. *d*-AM, BUP and MTH dose-dependently increased *d*-AM-appropriate responding. On average, the two higher doses of MTH occasioned 280% *d*-AM-appropriate responding, while the highest dose of BUP occassioned only 60% drug-appropriate responding. TRZ on average occasioned $\leq$ 33% *d*-AM-appropriate responding. These results suggest that the discriminative-stimulus effects of BUP overlap with those of *d*-AM to some extent, which is concordant with preclinical laboratory studies. Future studies should test higher doses of BUP (*e.g.,* 600 mg) to determine if they would produce more robust *d*-AM-like discriminative-stimulus.

EFFECTS OF D-AMPHETAMINE AND CAFFEINE UNDER A COCAINE DISCRIMINATION PROCEDURE IN HUMANS

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This study examined the pharmacological specificity of an oral cocaine discriminative stimulus in humans. Five male cocaine-abusing volunteers (2 Black/3 White) were trained to discriminate between cocaine HCl (80 mg/70 kg, P.O.) and placebo. Once the criterion for discrimination was met (*i.e., $\geq$80%* correct responding for four consecutive sessions), dose-effect curves were determined for the dopamine reuptake inhibitor cocaine (20, 40, 80, 120 mg/70 kg), the dopamine reuptake inhibitor d-amphetamine (5, 10, 20 mg/70 kg, P.O.) and the adenosine antagonist caffeine (150, 300, 600 mg/70 kg, P.O.). Cocaine produced dose-related increases in cocaine-appropriate responding with 20% cocaine-appropriate responding occurring at the 20 mg/70 kg dose and 80-100% cocaine-appropriate responding at the two highest doses. D-Amphetamine also produced a linear, dose related increase in cocaine appropriate responding, engendering 40% and 80% cocaine-appropriate responding at the 5 and 20 mg/70 kg doses, respectively. Caffeine produced cocaine-appropriate responding in a dose-related manner with 60, 60 and 90% cocaine-appropriate responding at the 150, 300 and 600 mg/70 kg doses, respectively. Each compound produced at least a trend toward increases in stimulant-like self-reports and vital signs. These preliminary results suggest that the cocaine discriminative stimulus (80 mg/70 kg) generalizes to d-amphetamine and caffeine.

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COCAINE CRAVING: AN EVALUATION ACROSS TREATMENT PHASES

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Although craving has been implicated as a factor in cocaine relapse and use, knowledge about its exact role in relation to drug taking is warranted. To address the issue, we examined the relationship between verbal reports of craving and actual cocaine use across different treatment phases using a longitudinal design. Subjects (n=32) were cocaine dependent patients who completed an inpatient chemical dependency program and then participated in an eight week outpatient relapse prevention program. Craving ratings and urine samples were collected at pre-treatment, at weekly treatment sessions, post-treatment, and at 2, 4, 8, 12, and 24 week follow-up. For purposes of data analysis, the sample was stratified by those who attained complete abstinence ("non-users"), those who had cocaine positive urines on fewer than 50% of the assessment occasions ("moderate users"), and those who used cocaine almost continuously across the assessment occasions ("heavy-users"). Results indicated significantly lower craving at the time of hospitalization compared to the first outpatient treatment session. The time x drug use interaction effect indicated significantly lower craving during outpatient treatment and follow-up phases in non-users compared to moderate and heavy users. The overall relationship between craving and total proportion of cocaine positive urines was significant ($r=.548$, $p<.001$). We will discuss these findings in relation to increasing our theoretical and practical knowledge about craving and cocaine use.

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PRELIMINARY REPORT OF BACLOFEN AS A COCAINE CRAVING MEDICATION

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Baclofen, a $GABA_B$ agonist that indirectly inhibits several neurotransmitter systems, may act to reduce episodic increases of catecholamine and glutamate release during acute cocaine craving. At Pizarro Treatment Center, ten cocaine abusers were treated with baclofen, in combination with group counseling (3 hours/week), for up to 16 weeks. All ten patients were initiated onto baclofen over a three day period, to a maximum dose of 20 mg t.i.d. Three patients had their dosages reduced due to side effects while the other seven patients remained on 60 mg/day for the duration of the treatment period, after which they were tapered from the medication over three days. Patient self-report and urine toxicology results demonstrated reduced cocaine craving and reduction in reduction in cocaine use in all but one patient over the 16 week treatment period. The most frequently reported side-effects from baclofen were drowsiness, nausea, headache, dizziness, and nightmares. All three patients who requested dose reductions had complained of drowsiness. No serious adverse events were reported during treatment due to either baclofen alone or baclofen/cocaine interaction. Thus, baclofen appears to be well tolerated and it may suppress cocaine craving during the early phases of cocaine withdrawal, when craving appears to be most disruptive to recovery. These findings support further evaluation of baclofen as a pharmacotherapy for cocaine dependence, using a double-blind, placebo-controlled design.

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SELEGILINE MODIFIES SUBJECTIVE EFFECTS OF EXPERIMENTALLY ADMINISTERED COCAINE

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Potential medication treatments for cocaine dependence have targeted alterations of "craving" for cocaine, withdrawal symptoms, and modification of cocaine's euphorigenic effects. Selegiline, at appropriate doses, is a selective MAO-B inhibitor not prone to producing hypertensive crises. Because selegiline blocks reuptake of catecholamines, it should increase available synaptic concentrations, reducing the deficit thought to develop after chronic cocaine use. This was hypothesized to reduce the change in synaptic catecholamine level produced acutely by cocaine administration, and in turn, the intensity of cocaine-induced euphoria. We tested this hypothesis by administering, in a single blind manner, cocaine to non-treatment seeking subjects receiving either placebo or selegihne 10mg/day.

Using repeated measures ANOVA with self-rated 'high' the primary outcome measures, a significant interaction ($p<.05$) between cocaine dose and saline vs cocaine was found, indicating that the difference between saline and cocaine infusion 'high' depended on the dose of cocaine. Simple effects showed that only the 40mg dose of cocaine produced significantly greater cocaine 'high' than did saline. There was no main effect of selegiline across both doses of cocaine. The ANOVA was then calculated after excluding data the 20mg cocaine and equivalent saline placebo. A selegiline vs placebo interaction with time ($p=.09$), indicating mat 'high' ratings in the placebo condition dropped more rapidly. Selegiline produced lower rated 'high' effects than placebo, after infusion of 40mg of cocaine ($p<.09$). These data suggest that selegiline shows potential as a medication treatment for cocaine dependence and should be investigated further.

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A CASE SERIES OF NEWLY ABSTINENT COCAINE-DEPENDENT OUTPATIENTS TREATED WITH PROPRANOLOL

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OBJECTIVE: This study evaluated the efficacy of propranolol in the outpatient treatment of cocaine dependence. METHODS: This was an open, pilot study involving 15 cocaine dependent patients presenting for outpatient treatment. Patients received between 60 and 100 mg of propranolol daily in two to three divided doses for eight weeks. In addition to medication, patients received weekly individual therapy and weekly group therapy. Primary outcome measures included treatment retention and qualitative urine toxicology screens. Secondary outcome measures included the Addiction Severity Index (ASI) and self reported cocaine use, recorded by timeline follow back. RESULTS: Eleven of fifteen patients (73%) completed the entire eight week trial. This retention rate was higher than the highest retention rate (50%) attained in three other similar open trials of medications for cocaine dependence conducted at our center. The percentage of benzoylecgonine negative urine samples submitted by the propranolol patients increased from 20% at screening to 60% at week eight. Seven of the fifteen patients (47%) achieved three or more weeks of confirmed abstinence. ASI Composite Drug and Composite Alcohol Scores declined significantly between baseline and week eight. Self reported cocaine use measured in both dollars spent for cocaine, and days of cocaine use in the prior 30 days, declined significantly between baseline and week eight. CONCLUSIONS: This preliminary study suggests that propranolol may be helpful in assisting cocaine dependent outpatients stay in treatment and attain abstinence. This trial is obviously limited by the small number of patients and the absence of a control group. A larger, double-blind, placebo-controlled trial is currently being planned to confirm these findings.

COGNITIVE FEATURES OF HUMAN DRUG CRAVING

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The Cocaine (CCQ-Now), Heroin (HCQ-Now), and Alcohol (ACQ-Now) Questionnaires have been developed to measure human drug craving in the current context based on the premise that craving consists of an admixture of urges and desires to use drugs, intent and planning to use drugs, anticipation of positive outcomes of drug use, anticipation of relief from withdrawal or negative outcomes, and lack of control over use. The Cognitive Theory of Drug Urges and Drug-Use Behavior conceptualizes drug cravings as responses supported by non-automatic cognitive processes activated in parallel with drug-use action schema in support of those automatized action schema or in support of attempts to block their execution. In addition, Alcohol Expectancy Theory posits that craving is mediated by expectancy, particularly in those situations in which persons experience emotional discomfort and lack confidence in their ability to stop drinking. Social Learning Theory also proposes that expectancies, namely outcome expectations and efficacy expectations, predict and explain drinking behavior and play a major role in alcohol craving. Thus, craving and expectations may be directly related to alcohol use, or craving may be indirectly associated with use because of the direct relationship of expectations and drinking, or there may be interactions between the two constructs. These three possibilities were evaluated using multiple regression models from secondary analyses of initial validity data using the new, 12-item ACQ-Now-Short Form. Identified cognitive schema contained elements of mood changes and intent to use alcohol linked to expectations of mood changes and perceived lack of efficacy in ability to quit. Findings supported a mixed, independent-mediator cognitive model because of the multidimensional nature of human drug craving.

PHENOMENOLOGY OF INPATIENT COCAINE WITHDRAWAL

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To better understand the psychological and physiological manifestations and time course of cocaine withdrawal, we prospectively evaluated 11 physically healthy, cocaine-dependent (DSM-IIIR), medication-free subjects with no other current substance dependence (except nicotine) who were housed on a closed research ward for 28 days. Ten were men, ten African-American, one white, mean [SD] age 31 [3.7] years, lifetime cocaine use 5.5 [4.1] years, using 3.5 [1.5] g/week, last use 13.1 [16.5] hours before admission. Pulse, blood pressure (BP), mood (Beck Depression Inventory, Profile of Mood States), cocaine craving (Minnesota Craving Scale, visual-analogue scales), and psychomotor performance (computerized digit symbol substitution test [DSST) were evaluated twice daily (a.m., p.m.> and sleep characteristics (St. Marys Sleep Questionnaire) daily. Pulse and BP stabilized in the normal range over the first 2-3 days, DSST performance and sleep duration and quality improved over the first 3-5 days, and mood scores (within normal range at admission) and cocaine craving progressively declined over the first 7-10 days. All variables remained stable over the last 2-3 weeks. These findings suggest that signs and symptoms of moderate cocaine withdrawal progressively normalize over 7-10 days without medication in an inpatient setting, and are not consistent with the previously reported triphasic model of outpatient cocaine withdrawal.

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COCAINE CLINICAL TRIALS DATABASE

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The Medications Development Division/NIDA is the primary sponsor of both drug discovery and clinical trials in the area of cocaine dependence. A database of all medication trials in cocaine dependence funded by MDD/NIDA through grants and contracts was developed to track MDD's current and completed cocaine clinical trials. The database contains the following information: grant or contract title, principal investigator, objective, trial status (planning, ongoing, completed), characterization of subjects, dose and drug, study design, trial duration, outcome measures, instruments, statistical analysis techniques, side effects, sample size, number of completers, publications, and conclusions/comments. In addition to NIDA monitoring of its funded research, this mechanism has the potential to facilitate collaboration among investigators. The database presented herein currently contains 58 trials involving 30 different compounds.

COCALIZATION: THE STANDARD LOW DOSE OF ORAL COCAINE USED AS SUBSTITUTION THERAPY IN COCAINE DEPENDENCE

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Some reports have demonstrated that use of oral cocaine (OC) as coca infusions (CI) or coca tablets (CT), in standard low doses (cocalization method as substitution therapy), reduce the average of relapses (AR) in chronic smoke cocaine (coca paste) addicts.

Since 1991, 51 volunteers (mean 25.5 years; males; 3 relapses per week; >1 year of use), were treated with oral cocaine (CI/CT).

Three studies have been published: a) 23 subjects, open trial (3 months to 1 year), 4.35 AR month prior treatment with 20-30 mg of OC/CI, reduce AR to 1.22 a month; b) 8 subjects, double blind trial (5 weeks), 4.3 AR week prior treatment with 20-60 mg OC/CT, reduce AR to 0.70 week; c) 20 subjects, open controlled trial (3 months), 4.3 AR week prior treatment with 20-60 mg OC/CT, reduce AR to 0.3 week. Urine tests (Abuscreen Ontrak/TDx) were used during treatment. Results suggest that oral cocaine in standard low doses (Cocalization method) could be an efficient treatment ($P<0.01$) for reducing the relapse average in chronic cocaine dependents.

HIGHER DOSES OF MAZINDOL FOR TREATMENT OF COCAINE DEPENDENCE

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The only placebo-controlled study of mazindol in primary cocaine dependent patients randomized 43 patients to mazindol (2 mg po QD) vs. placebo treatment for six weeks (Stine *et al.,* 1995). This study demonstrated no difference between the two groups but was limited by me single 2 mg dose. Although higher doses of mazindol might be useful in treating cocaine abuse, acute combinations of mazindol and cocaine were found in human laboratory to have adverse physiological effects (Preston *et al.,* 1993). We are testing the hypothesis that mazindol doses higher than 2 mg may be effective. The general method is the same as in the above studies but higher doses of mazindol are used in a six week treatment study and blood pressure is measured weekly. For those patients who have positive urine toxicology screens for cocaine after two weeks of treatment the dose of mazindol increases by 2 mg each week to a maximum of 8 mg per day unless abstinence is attained. The dose is held at the point of abstinence. Preliminary analysis of data from the 11 subjects (5 mazindol, 6 placebo) over the first six weeks of treatment is reported. The average retention for both groups was five weeks. Average maximum dose was 4.5 mg (1 patient on 6 mg and 1 on 8 mg). There are no differences in percent positive urines (93% mazindol, 81% placebo) or quantitative cocaine toxicologies (mazindol-228.15 ± 39.2; placebo-187.99 ± 46.5). Blood pressure (percent baseline) was not elevated (diastolic, mazindol-101%, placebo-97%; systolic, mazindol-108%, placebo-104%) and there were no adverse events and no drop outs due to side effects. The data do not suggest mazindol is effective in this population even at higher doses, but it appears to be tolerated at the doses used so far. This study will continue until 20 subjects in each group are completed. Interpretation of the results to date are limited by small number of subjects and imbalance in the groups in respect to age (29 ± 3 vs. 43 ± 3) and Addiction Severity Index (ASI) psychiatric severity (0.34 ± 0.10 vs. 0.06 ±.04) for mazindol vs. placebo respectively. If there is any indication of efficacy a larger clinical trial will be conducted.

A META-ANALYSIS OF THE STATISTICAL POWER OF THE PHYSIOLOGICAL AND SUBJECTIVE EFFECTS OF COCAINE

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There are a number of techniques which can be used to analyze within session time course effects of drugs, such as raw scores, peak and area under the curve. The present study uses meta-analysis to examine the statistical power of 15 techniques in six investigations of the potential pharmacological interaction of different compounds with the effects of cocaine. Power estimates are derived from comparison of placebo and two active doses of cocaine for each study. Power analysis is crucial to the planning and design of efficient and effective studies. Information on effect sizes derived from meta-analyses can be used to provide good estimates of power for future research. This study also illustrates a method of meta-analysis that can be used to estimate effect sizes for power calculations. Physiological measures had significantly greater effect sizes than subjective measures for peak (1.16 vs. 0.97), AUC (1.31 vs. 0.87) and time course analyses (1.39 vs. 0.90). AUC and time course analyses were significantly more powerful than peak analyses for objective measures. The robustness of effect sizes in these small N 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 studies examining the potential pharmacological interaction of different compounds with the effects of cocaine.

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AIDS RISK INVENTORY (ARI): A STRUCTURED INTERVIEW FOR ASSESSING RISK OF HIV INFECTION IN A POPULATION OF DRUG ABUSERS.

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Reducing transmission of HIV infection among drug-abusing populations is a major focus of drug abuse treatment and research. The availability of reliable and valid assessment allowing quantification of sexual and drug-use behaviors associated with HIV infection is then critical. The self-administered Risk for AIDS Behavior (RAB) is in widespread use; however, our analysis of data collected with the RAB during clinical trials with 273 subjects documents limited variability of scores at treatment entry, and suggests that the RAB may not be sufficiently sensitive to detect clinically meaningful change. In response to the need for an instrument that can better discriminate between subjects with high- and low-risk of HIV infection, as well as reliably assess change in behavioral patterns associated with high risk of HIV infection during drug abuse treatments, we developed the AIDS Risk Inventory (ARI). The ARI is a structured interview containing questions about behaviors associated with drug use, sexual practices, and general knowledge of AIDS prevention. This new instrument was pilot tested to assess its feasibility of use, external validity, and ability to discriminate between high- and low-risk drug abusers. Our preliminary results show that the ARI can be successfully used in a clinical trial settings. The interview format of this method allows good comprehensibility of questions and helps to maintain clients' interest. A "tree-like" structure of the ARI allows for in-depth investigation of behaviors that are client-specific, and, on average, results in a short time of interviewing. We will continue to test the ARI in order to evaluate its psychometric characteristics and standardization of scores, as well as its reliability, validity, and sensitivity to detect change.

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PRELIMINARY REPORT ON SEXUAL HIV RISK BEHAVIORS AMONG URBAN GAY MALE METHAMPHETAMINE ABUSERS

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Epidemiological reports have documented a 200% increase in emergency room mentions and drug treatment admissions related to methamphetamine in Los Angeles since 1992. Local treatment providers are concerned about HIV-related high risk sexual behavior among urban gay males in the context of methamphetamine abuse. To test the hypothesis that gay male methamphetamine abusers engage in high-risk sexual acts, we examined data collected from 16 gay and bisexual male methamphetamine abusers between 1989 and 1993. Data on sexual behavior were obtained using the NIDA/WAVE questionnaire, a semi-structured interview of HIV-related risk behaviors. Findings indicated that 75% of respondents were concerned about their sexual behavior. Drug use was frequently combined with sexual activity. Fifty percent (50%) of respondents reported unprotected anal-receptive sex, and 62.5% reported anal-insertive sex without a condom over the past 12 months. Further, 56.3% of participants indicated having had sex with someone who had HIV over the past 12 months. Mean number of sex-partners over the past 12 months was 31 (SD=41). HIV transmission risk seems extremely high for this population.

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HIV RISK FACTORS AMONG GAY, BISEXUAL, LESBIAN AND TRANSGENDER STREET USERS

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The Van Ness Recovery House (VNRH) is a non-profit corporation dedicated to serving the needs of gay, bisexual, lesbian, and transgender substance misusers. The VNRH provides a 20-bed residential facility, day treatment, sober living and job training. The Prevention Division of the VNRH offers street outreach, counseling interventions, immediate linkage to services, peer-facilitated education and support groups, community workshops, and art exploration groups. This study examines a community-based outreach and intervention program that targets high-risk gay, bisexual, lesbian and transgender drug users on the streets of Hollywood, California. The intervention program was based on a harm reduction model, measuring outcome as any psychosocial, psychological or physical reduction in the harm that results from drug use. In 1995-1996, 4,040 active users were contacted; of those, indepth interventions were conducted with 1,415 drug users. Street users contacted through this project were predominately gay (48%) and bisexual (30%) men. Twenty-four percent of street users were injectors. Injectors were more likely than non-injectors to be bisexual Injectors were more likely to be Caucasian/white than non-injectors. Approximately half (49%) of non-injectors and 68% of injectors engaged in sex work; injectors were less likely to always use condoms than non-injectors. The most commonly used drug was crystal methamphetamine. Findings are useful in developing intervention programs for hard-to-reach gay, bisexual, lesbian and transgender drug users.

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HIV-RELATED RISK BEHAVIORS AMONG HOMOSEXUAL AND HETEROSEXUAL RECENT ARRESTEES

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This project, as part of the California Drug Use Forecasting Project (DUF), obtained descriptive information about high risk HIV transmission behaviors from a sample of 881 men arrested in Los Angeles County between 7/1/94 and 4/30/95. Respondents were classified as either those who have sex with men (MSM=3.7%) or those who do not (non-MSM=96.3%).

The MSM group reported a significantly higher percent of HIV-risk behaviors on nearly all measures. MSMs were more likely to report "feeling addicted in me past year" to methamphetamine (9%) and PCP (6%) than non-MSMs (3% and 1%). The two groups also differed in assessing their own HIV-related risk behaviors, with 60% of the MSMs rating their chances of getting AIDS as either "very likely" or "likely" compared to 17% of the non-MSMs ($p<.01$). More MSMs admitted to being tested for HIV (81%) and to being HIV sero-positive (19%) than the non-MSMs (54% and 1%; $p<.01$ respectively). They were also more likely to share needles (16% vs 7%) and pay for sex with drugs or money (29% vs 3%) than their counterparts. MSMs reported greater frequency of psychiatric and psychological problems, including suicide attempts and psychiatric hospitalizations, and higher incidence of gonorrhea, syphilis, tuberculosis, and hepatitis. They were also more likely to have been raped or beaten, to report illegal income, and to need public assistance than the non-MSMs.

Results of this survey demonstrate the need for effective interventions aimed at substance abuse, psychiatric problems, and HIV-risk related behaviors, in this especially vulnerable, high risk population.

AIDS RISK FACTORS AND GENDER DIFFERENCES OF CRACK SMOKERS

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A crack smoking lifestyle is linked to increased risky sexual behaviors and the rise in HIV infection. This study presents AIDS risk factors and gender differences of 75 crack abusing or dependent clients during the six months prior to residential or day treatment as measured by the AIDS Risk Assessment for Crack Smokers (ARA-C) instrument. Clients were 76% male, 61% black, 39% white, with an average age of 35.8 (SD=6.6) years. Results: Frequency of crack smoking averaged 3-4 times per week and 78% reported sex after smoking crack, with condoms used "sometimes". Clients smoked crack with 72% of the 5.1 (SD=8.5) different sex partners reported. Thirty-eight percent used crack with a sex partner, 24% with a date, and 28% with a "trick". Frequency of sex after smoking crack was 2-3 times per month, which did not differ from sex when not smoking crack. Women reported more sex after smoking crack (1-2 times per week) than men (2-3 times per month)(p=.02). Single sexual encounters were more frequent after smoking crack (49%) than when not smoking crack (28%), (p=.05). Trading Sex and Crack: Seventy percent traded sex for crack or crack for sex, with condoms used "sometimes". Fifty percent admitted to vaginal and oral sex and 1.4% to anal. Clients reported trading sex for crack 3.0 (12.2) times and crack for sex 2.5 (1.5) times in the past six months, with women 33 times more likely to trade sex for crack than men, 11.6 (SD=23.5) vs. .35 (SD=.99) times, respectively (p=.001). Crack and Self-control: When smoking crack, clients reported less shyness, more desire for sex, less self-control, less sexual enjoyment, and more sexual assertiveness. Men were more likely than women to "come on" to others sexually (p=.02) and desire sex (p=.01) after smoking crack. Men were more likely than women to talk about sex with their regular sex partner and a "trick" (p=.05). Conclusion. This study revealed many AIDS risk factors associated with crack smoking and sexual behaviors. Findings will be discussed in terms of a gender specific AIDS prevention program for crack smokers and the use of the ARA-C as an AIDS risk factor measure of change. Supported by CSAT-7HD8TI00971 and NIDA-RO1DAD8475 grants.

HIV INFECTION RISKS AMONG HOMELESS, MENTALLY ILL CHEMICAL ABUSING MEN

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Homeless, mentally ill, chemical abusing (HMICA) men lack the minimal amenities needed to live in main stream society: housing, a job, and a support network. This paper evaluates the relative role of homelessness, mental illness and chemical abuse in elevating the risk of HIV infection. The sample consisted of 315 HMICA men recruited for treatment in community based residential programs in New York City between September,. 1993 and January, 1995. The history of psychopathology, substance abuse, homelessness, HIV related risk behaviors and HIV status was obtained by interview. HIV seropositivity was checked against medical charts. Our findings show a rather high rate of HIV seropositivity among HMICA (12.45%). The 25% of HMICAs who had used drugs intravenously were at a significantly higher risk of HIV infection (23.5%). Of the three HMICA conditions, the experience of serious depression correlated most strongly with the highly risky IVDU behavior of repeated episodes of needle sharing with strangers, with prostitutes and with partners known to have shared needles with others. The majority of HMICAs reported risky sexual conduct which was strongly correlated with homelessness. The more severe homelessness was, the higher was the risk of sex with partners who traded sex for money or drugs, with strangers, with IVDU's and without using condoms. Mental illness and chemical abuse characteristics were not found to be significantly related to risky sexual conduct. ACKNOWLEDGMENTS: Supported by NIDA Grant DA 06968

AIDS RISK BEHAVIORS AMONG COCAINE OR HEROIN DEPENDENT SUBJECTS IN PHARMACOTHERAPY TRIALS

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OBIECTIVE: To describe the relationship between drug use and self-report of AIDS risk behaviors in pharmacotberapy study subjects. METHOD: In two separate pharmacotherapy trials for the treatment of cocaine or opioid dependence, 80 subjects were interviewed with the AIDS Risk Assessment Battery (RAB) which has both Drug Risk and Sex Risk items. The cocaine-dependent (COC) subjects were in an outpatient trial of fluoxetine treatment. The heroin-dependent (HER) subjects were in a trial of methadone treatment to facilitate isoniazid chemoprophylaxis for tuberculosis. COC subjects' (n=40) mean (±SD) age was 38.5 (±5.8); they were 40.4% female, 65% African-American, and 10.6% human immunodeficiency virus (HIV) positive. HER subjects' (n=40) mean age was 42.1 (±5.0); they were 45.0% female, 40.0% African-American; only HIV negative Ss were studied. RESULTS: Intake cocaine use was significantly correlated (Pearson r=.393, p=.013) with RAB Sex Risk score in HER Ss; in COC Ss, the correlation was .259, p=.106. Intake heroin use, however, was not significantly correlated with Sex Risk score in HER Ss (r=.206, p=.209). In HER Ss, length of time in the study was associated with significant decrease in RAB Total score (repeated measures ANOVA, F=4.56, p=.006) and in RAB Drug Risk score (F=4.79, p=.004), with a trend toward a decrease in Sex Risk, score (F=2.22, p=.094). CONCLUSIONS: Sexual risk behavior is correlated with cocaine use, whether Ss are heroin or cocaine dependent. AIDS risk behaviors in HER Ss decrease with duration of time in pharmacotherapy trials.

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HEROIN SNIFFERS

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The concern that syringe exchange (SE) will lead to illicit drug injection-particularly, that SE will lead new persons to begin injecting drugs- has been frequently voiced by opponents of SE, yet no studies to date have found such an effect. Nevertheless, the question of why persons would begin injecting drugs even though knowing about the risk of AIDS, is an important area for harm reduction inquiry. As part of the larger New York City SE evaluation study, we conducted a substudy of 101 heroin "sniffers," whose non-injected use of heroin was sufficient to seek drug abuse treatment. The study sample was stratified into two groups: those who never injected and those who had a history of injection. Results: Of the 101 persons interviewed 32% were women; 54% of the sample were Latino. The average age was 34 years. Fifty-six (55%) had never injected. Those who had never injected were less likely to have spent time in prison ($p<.001$); less likely to be self-employed ($p<.05$); and more likely to currently receive welfare benefits ($p<.05$). No significant differences were observed for race, gender or age. Of those who had a history of injecting (45%), 56% had not injected in the last 30 days and were most likely to sniff heroin ($p<.05$). Ethnographic data indicate the main reason given for stopping injecting was fear of contracting AIDS and the main reason for never injecting was fear of needles. Correlates associated with making a transition from injecting to sniffing and factors associated with never injecting will presented along with ethnographic data.

A RISK REDUCTION PROGRAM FOR HIV-SEROPOSITIVE INJECTION DRUG USERS: PRELIMINARY FINDINGS

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Impairment in cognitive functioning experienced by HIV-seropositive cocaine- and opioid-dependent patients may impede their ability to benefit from standard treatments. We report on an open-label trial of bupropion (150 mg/day) provided within the context of a specialized Risk Reduction Therapy (RRT) for HIV-seropositive cocaine-abusing methadone patients. RRT attempts to meet the special needs of HIV-seropositive drug users by using cognitive remediation strategies -- traditionally used in rehabilitation settings with patients with traumatic brain injury -- in order to teach risk reduction skills to these potentially cognitive impaired HIV-positive injection drug users. Participants were 18 cocaine- and opioid-dependent HIV-seropositives; eight received standard treatment (methadone plus standard skills training group); ten received the specialized program. Cocaine use, opiate use, cocaine craving, depression, and ASI drug severity scores decreased significantly only for patients completing the specialized Risk Reduction Program. Decreases in other high risk behaviors, such as needle sharing and unsafe sexual practices were also reported. Additional pharmacotherapeutic agents with the potential to address both cocaine use and cognitive impairment are currently being investigated in the context of this specialized program.

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COMPARING CHANGE IN HIV RISK BEHAVIORS BETWEEN PEER COUNSELING AND STANDARD INTERVENTIONS

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The St. Louis NIDA Cooperative Agreement for AIDS Community Based Outreach/Intervention Program enrolls crack cocaine users and IDU's from the inner city into an HIV prevention program in order to test the effectiveness of a Peer Counseling intervention program. Study subjects are randomly assigned to either a Standard intervention or to the Peer Counseling intervention. The Standard intervention consists of street outreach and HIV antibody testing and counseling while the Peer Counseling intervention includes the same components plus four weekly peer group counseling sessions which ate conducted by substance abusers in recovery, covering: 1) Life Problem Management, 2) Drug Awareness, 3) HIV Education, and 4) Denial and Sexual Behaviors. Data from both groups are collected at baseline and three months later. HIV testing and counseling are also performed at each time period. The sample (N=339) is 43% female, 90% African American, 51% have at least a high school education, and 40% have never been married. Preliminary results indicate significant reductions in drug use for both Standard and Peer Counseling respondents. Sexual risk behaviors (e.g. the number of sexual partners) also decreased for both groups, though the Peer Intervention had a greater reduction. These results will be examined using both univariate and multivariate statistical techniques. So far both the Standard and Peer interventions appear promising.

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HIV PREVENTION EDUCATION AND TESTING FOR INTRAVENOUS DRUG ABUSERS: CHANGES IN DRUG ABUSE AND SEX BEHAVIORS

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One hundred sixty-nine male, veteran, intravenous drug users receiving substance abuse treatment, participated in an HIV prevention education and HIV testing research study. Subjects attended five 1 and 1/2 hour HIV prevention education sessions which focused on reducing HIV-related risk behaviors. Follow-up visits were scheduled every three months. Comparisons on study outcome measures were made between baseline, follow-up Wave 1 (3 or 6 mos. follow-up) and Wave 2 (9, 12 or 15 mos.) using the last observation carried forward method (LOCF). Analyses indicated that significant reductions in HIV risk behaviors primarily involved changes in IV drug use behaviors. Specifically, subjects reported significant reductions from baseline to follow-up in both IV heroin and IV cocaine use ($p<.01$), and number of needle-sharing partners ($p<.01$). Although not significant, an increase in needle cleaning via bleach method was evident. Results also indicated a reduced incidence of receiving payment for sex ($p<.01$) and an increased frequency of condom use ($p<.01$). No significant changes were found in the number of sexual partners or frequency of sexual contacts. Following the HIV prevention education, significant improvements were demonstrated in the subjects' level of accurate HIV risk reduction information ($p<.01$) and in their attitude towards engaging in risk reduction behaviors ($p<.01$). These results suggest that the HIV prevention education appeared effective in reducing some drug use and sexual behaviors associated with HIV risk, and improved level of HIV knowledge and attitudes towards behavior change.

REACHING THE UNREACHABLE: OUT OF TREATMENT INJECTION DRUG USERS

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The St. Louis EachOneTeachOne (EOTO) project is a NIDA-funded Cooperative Agreement aimed at examining rates of HIV risk behaviors and studying HIV risk reduction interventions among out-of-treatment injection and crack cocaine drug users. This paper uses data collected during the first year of recruitment/enrollment to document the effect of street outreach on HIV risk behavior involvement. The major findings are that: 1) men reported more HIV risk behaviors than did women, but the results failed to show striking racial/ethnic differences; 2) we successfully enrolled women in spite of the fact that our women street contacts were largely ineligible to enroll in EOTO; 3) actual EOTO enrollees, compared with all street contacts and eligible street contacts, engaged in fewer HIV risk behaviors. These results imply that strategies in addition to street outreach are needed to enlist more individuals, particularly whites and women who are engaging in the highest risk drug and sexual behaviors.

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COMPARISONS OF DRUG-FREE AND METHADONE COUNSELORS WHO TREAT SUBSTANCE ABUSERS WITH HIV

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Drug abusers with HIV pose demanding medical and social challenges to counselors who treat them. In a 2-year, NIDA-funded project, designed to evaluate a structured HIV-specific drug counseling manual, 136 counselors from 16 methadone and 16 drug-free clinics completed baseline surveys rating their job satisfaction, counseling activities, job "burnout," and HIV knowledge. We analyzed dependent measures by type of clinic (methadone vs drug free). Group comparisons were made using the Survey DAta ANalysis (RTI, 1993) to account for intraclass correlations. Results indicated that counselors from drug-free settings (DF) were significantly more satisfied with their jobs ($\underline{M}_{DF}$=5.27, $\underline{SE}$=.08; $\underline{M}_{Meth}$= 4.87, $\underline{SE}$ =.08; $\underline{t}$(104)=2.92, $\underline{p}$<.01) than methadone counselors (Meth). DFs felt they had more personal control in their work settings ($\underline{M}_{DF}$=4.54, $\underline{SE}$=.08; $\underline{M}_{Meth}$=4.54, $\underline{SE}$=.15; $\underline{t}$=2.23. $\underline{p}$<05)) and were less pessimistic about their jobs ($\underline{M}_{DF}$=3.90, $\underline{SE}$=.05; $\underline{M}_{Meth}$=3.90, $\underline{SE}$=.06; $\underline{t}$=2.29, p<.01) than Meths, but reported slightly more job-related depression $\underline{M}_{DF}$=2.15, $\underline{SE}$=.06; $\underline{M}_{Meth}$=1.92, $\underline{SE}$=.06, $\underline{p}$<.05). DFs felt their ideal caseloads would allow an 8% increase over their current number of patients; Meths reported their current caseloads to be 21% more than ideal ($\underline{M}_{DF}$=.14, $\underline{SE}$=1.81; $\underline{M}_{Meth}$= 10.48, $\underline{SE}$=1.32; $\underline{t}$=2.81, $\underline{p}$<.01). Both groups appeared to have limited HIV knowledge, with the DFs correctly answering an average of 11.1 of 20 questions and scoring only slightly better ($\underline{M}_{DF}$=11.1, $\underline{SE}$=0.3; $\underline{M}_{Meth}$=10.4, $\underline{SE}$=0.3) than the Meths who averaged 10.4 correct answers. This project demonstrates the need for improved education, especially about substance abusers with HIV, in an effort to reduce the job stress and "burnout" among counselors who treat this difficult addict population.

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TREATMENT READINESS IN SUBSTANCE ABUSERS WITH HIV INFECTION

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We examined readiness to change in an ongoing randomized trial of case management for HIV-infected substance abusers. Data come from the fist 167 participants, recruited from medical wards of a hospital. We examined (1) level of motivation for changing substance use for primary drug of choice, measured by the University of Rhode Island Change Assessment (URICA) scale, and (2) relationship of readiness to change to drug use and HIV transmission risks. Of the 167 participants 73% were men, 41% were African American and 44% Caucasian, and mean age was 39 years. Most were homeless (25%) or in a hotel (37%). A "Readiness to Change" measure using URICA scores were significantly correlated with psychiatric and drug use severity, and an index of sexual risks. We conclude that readiness to change may be a helpful concept in understanding HIV infected substance abusers. Future analyses will examine how readiness to change predicts response to case management.

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MEDICATION SIDE EFFECTS IN THE TREATMENT OF DRUG DEPENDENCE: DO THEY AFFECT SUBJECT RETENTION?

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Side effects of medications used in the treatment of cocaine dependent subjects (with and without concurrent opiate dependence) ate reported with variable incidence. In this study, we examined the patterns of reported side effects (type, frequency, and dose response) and their relationship to retention. Subjects (n=328) participated in a series of double-blind outpatient research studies. The medications used were fluoxetine, methylphenidate and risperidone in cocaine dependent subjects, and fluoxetine + methadone or risperidone + methadone in cocaine + opiate dependent subjects, Side effect data were collected using the Weekly SelfReport of Drug Effects questionnaire, a list of 29 symptoms rated on a binomial scale (Y/N). Two thousand, four hundred and seventy-one (2,471) forms were evaluated. For analyses purposes, side effects were categorized by organ system (positive psychiatric response, negative psychiatric response, gastrointestinal, respiratory, central nervous system, cardiovascular, and miscellaneous), and averages were compiled for each study by dose (separate and combined averages versus placebo) and completion status. It was found that side effects were generally not useful predictors of retention, treatment success or treatment failure in these behavioral based medication interventions.

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PATIENT RETENTION IN A MEDICAL PRACTICE FOR SUBSTANCE ABUSE

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Medically ill addicts and alcoholics need lifetime medical care. Because of the AIDS epidemic, the number of such patients is increasing and their needs are for a medically oriented, rather than psychosocially oriented program. We aimed to create such a program with a high level of retention and visit compliance. The Comprehensive Care Practice (CCP) opened in June 1994 to treat ill addicts and alcoholics. Staff were specially trained to take care of patients with addiction. Patients did not need to be in drug treatment to be seen. At the end of 57 weeks, 194 patients were enrolled, of which 125 were in drug treatment. Mean age was 38.0, 65% were male and 85 patients were HIV+. Patient data were submitted to a Kaplan Meier survival analysis to give mean weeks of survival. There was 84% survival for patients in substance abuse treatment, compared to 76% for patients not in substance abuse treatment; the difference was not significant. For patients in treatment, survival was the same for the three treatments analyzed-AA/NA, methadone and outpatient counseling. Overall, the visit show-rate was 78%, with an even higher 82% if missed first visits are excluded. In conclusion, medically ill addicts can be treated successfully in a dedicated outpatient practice with a rate of retention higher than that reported for substance abuse programs. The rate of retention is not affected by substance abuse treatment external to the practice.

KNOWLEDGE OF TUBERCULOSIS AMONG DRUG USERS: RELATIONSHIP TO TUBERCULIN STATUS AND SCREENING RETURN RATES

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The knowledge, attitudes, and perceptions of active drug users of tuberculosis (TB) may be important in the success of TB programs targeted to this high prevalence group. Participants at a New York City syringe exchange were offered TB skin testing (TST), were interviewed and received $15.00 upon returning for skin test interpretation. Through 1/31/96, 566/610 (93%) IDUs returned for TST readings. 86% had been previously TB skin tested (80% ≤ 2 yrs), 13% reported prior reactive TSTs, 12% partial or complete prior TB preventive therapy. 92% knew that TB is contagious, 74% that TB is treatable, and 72% that preventive therapy existed. However, 70% thought a reactive TST implied infectivity, 30% thought TB could be treated without a medical doctor, 28% that HIV-related TB could not be treated, 15% felt home remedies could prevent TB, and 7% felt nonprescription medications could cure TB. Tuberculin reaction rates were 14% ≥ 10mm and 4% 5-9mm. Those with prior positive TST less frequently thought that a reactive implied infectivity (16 vs 29%; OR 1.9; 95% CI 1.05-3.3; p=.01 perhaps due to prior testing related education. In a logistic regression no knowledge factors were significantly associated with rates of return. Those with self-reported prior positive PPD/TB therapy were more likely to have PPD reactions ≥ 5 mm (OR, 12.5; 95% CI; 6.6-23.7). Reliance on self reported data alone would have missed 50% of those with reactive TSTs. Excluding those with self-reported prior reactive TSTs from screening would have reduced number of needed skin tests by 15%. IDU possess reasonable understanding of TB transmission, prevention and treatment. However, misunderstandings exist between TB infection and disease and knowledge of TB transmission is suboptimal in underscoring the need for TB education in this population. Self-reported data on prior reactive skin tests are predictive of actual skin test reactivity.

`SHOTGUNNING' AS A DRUG USE PRACTICE AND ITS RELATIONSHIP TO TUBERCULOSIS

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There has been a rise in the inhalation route of drug use. `Shotgunning' drugs refers to inhaling smoke and then exhaling it into another individual's mouth, a practice with the potential for the efficient transmission of respiratory pathogens. Drug users are at high risk for TB infection, an association that has been noted for non-injection as well as injection users. We characterize `shotgunning' as a drug use practice and examine its relationship to tuberculous infection. Participants at a New York City syringe exchange program and an inpatient detox program were offered PPD and anergy skin testing. Those consenting were interviewed, offered HIV testing, and received $15.00 upon returning for skin test interpretation, Of 354 drug injectors recruited between 7/95-1/96, 55%, 32%, and 20% injected heroin, cocaine or both; 52% used one or more inhalational routes. 59 (16.7%) overall reported shotgunning among crack users and 59% of these report both exhaling the smoke into others and inhaling the smoke from others. 68% of those who shotgun, report doing so while smoking crack, 41% with marijuana, 2% with smoked heroin; 8.5% shotgun with _ 1 drug. Users report shotgunning with friends (49%), sex partners (19%), and with 'tricks' (12%). Reasons cited for shotgunning were:intimacy, conserving drugs, and getting a better high. Those who shotgun were younger (mean 30.4 vs. 35.9 y); more often female (p=0.017, OR 1.9); and more often white (p<0.016, OR 2.0). Tuberculin reaction rates identified during the study period were 14% >=10mm, 2% 5-9mm, with a 0.4% rate of active TB. PPD positivity rates did not differ among those who did or did not shotgun. No association with PPD reactivity was noted. However the potential exists for shotgunning being a route of TB transmission in a population at risk for the reactivation of latent TB infection, further underscoring both the need for education of drug users about the risks of specific drug use practices and the need for TB preventive therapy in active drug users.

FACTORS ASSOCIATED WITH TUBERCULIN REACTIVITY AMONG PARTICIPANTS AT A SYRINGE EXCHANGE PROGRAM.

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Drug users are at high risk of tuberculous (TB) infection. Identifying subgroups of active drug users with a greater prevalence of TB infection may be valuable in guiding the development of TB services and in targeting interventions to disrupt transmission. Participants at a New York City syringe exchange were offered PPD testing, were interviewed and received $15.00 upon returning for skin test interpretation. A positive PPD was defined as induration ≥ 10 mm in HIV-negative patients and ≥ 5 mm in all others. From 3/95-1/96, 610/650 (94%) consented to screening. 566 (93%) returned for skin test readings. The age range was 16-64 y, 34% were female, 55% nonwhite, 87% were born in the continental US, 35% were unstably housed, 67% had ≥ 1 incarcerations, 15% had histories of isoniazid/TB therapy and 18% were HIV-infected. 73% had previously been in drug treatment and 39% were currently in drug treatment. 463 (82%) were injection drug users (IDUs) and 71% of these had a history of injecting drugs ≥ 5 years. PPD reaction rates were 4% 5-9 mm, 14% ≥ 10 mm, 9% anergic, and 3.5% were both PPD positive and HIV-infected. In a logistic regression model, injection drug use ≥ 5 years (OR, 12; CI, 6.6-23.7; p = .0001), previous isoniazid/TB therapy (OR, 3.1; 1.5-6.7; p =.003), black race (OR, 2.5; CI, 1.3-5; p =.005), and being born in the continental US (OR, 0.4; CI, 0.2-0.9; p =.03) were independently associated with PPD positivity. In summary, a high frequency of participants had both TB and HIV infection underscoring the need for TB and HIV prevention in needle exchange programs. Using a ≥ 5 mm cutpoint resulted in only modest increase in PPD positivity. The identification of subgroups with higher or lesser risk of TB infection may facilitate the clinical decision for isoniazid prophylaxis among drug users, especially those who are anergic.

ASTHMA AND HYPERTENSION AND RELATIONSHIP TO ROUTE OF USE IN SINGLE AND POLYDRUG ABUSERS

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The purpose of this study is to determine the prevalence of asthma and hypertension in 1,978 admissions to inpatient detoxification (detox) treatment. The prevalences of these illnesses will be determined according to age, gender, race, and route of administration and compared for these characterizations within this sample and to the general population. In previous research, it has been determined that individuals who smoke or inhale drugs of abuse also have more asthma and other respiratory disorders. Hypertension is associated with the use of alcohol. However, these studies were not carried out on samples as large as the one in this study. The sample used in this study is 1,978 consecutive admissions during one calendar year to a hospital inpatient drug detox unit. Information on drugs of abuse, routes of use, and current medical problems were abstracted from the drug and medical histories obtained on admission. Demographic data were also obtained from these histories. Controlling for age, race, gender, drugs abused and routes of use, the numbers of admissions reporting hypertension and asthma will be compared to numbers reporting no medical problems. Appropriate statistical analyses will be employed to assess the association among demographic characteristics, substances abused, routes of administration, and the presence or absence of asthma or hypertension.

ERYTHROCYTHEMIA ("BLOOD DOPING") AFTER INTRANASAL COCAINE ADMINISTRATION TO HEALTHY HUMAN SUBJECTS

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Cocaine is among the most dangerous drugs of abuse during sport due to its acute cardiotoxicity. Erythrocythemia ("blood doping") induced by cocaine has been reported in an animal model but not previously studied in human subjects. Given the incremental potential for medical morbidity in athletes from such a drug-related effect, we measured sequential hematologic parameters after a moderate dose of cocaine administered intranasally to healthy human subjects. Fourteen healthy male volunteers, 21-35 years of age, with reported sporadic prior cocaine use participated after informed consent. Vital signs and electrocardiographs were continuously monitored before and for 90 minutes after intranasal cocaine administration (0.90 mg/kg) via a modified snort-stick device. Blood samples were collected every 10 minutes for measurement of hematologic parameters. Hemoglobin concentration and hematocrit significantly increased at 20 minutes after cocaine use, peaked at 40 minutes and persisted to 60 minutes ($p=0.001$) by which time changes in heart rate and blood pressure had resolved. White blood cell and platelet counts were unaffected. These data demonstrate that sustained erythrocythemia ("blood doping") occurs in healthy humans following a moderate dose of cocaine and this effect may contribute to medical morbidity during sport.

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ACUTE EFFECTS OF INHALED COCAINE BASE AND INTRAVENOUS COCAINE HCI ON AIRWAY AND PULMONARY VASCULAR RESISTANCE

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Smoked cocaine base is associated with a number of pulmonary consequences, including symptoms of wheezing, acute asthma attacks and diffusion impairment in the lung. To investigate the mechanism of these effects, we compared the acute effects of inhaled cocaine base (38.5±2.3 [SEM] mg) and/or intravenous (IV) cocaine HCl (30.0±2.0 mg) with those of inhaled "placebo" (2.3 ± 0.9 mg cocaine base -a subphysiologic dose) and/or IV saline (IV placebo) on airway resistance (Raw) (measured by whole-body plethysmography), pulmonary artery pressure (PAP), cardiac output and pulmonary vascular resistance (PVR) (assessed by Doppler echocardiography), heart rate (HR) and self-rated level of intoxication ("high") in 14 healthy, nonsasthmatic current crack-smoking subjects, 34-48 yrs of age, using a single-blind cross-over study. Cocaine base was inhaled using a thermostatically controlled delivery device (Hatsukami *et al.* Pharmacol Biochem Behav 1990; 36: 1-7). Both inhaled and IV cocaine caused comparable, signficant ($p<0.05$) peak levels of "high" (6.±0.7 and 7.3±0.8, respectively, on 0-10 scale) and % increases from baseline in HR (29.6±2.9 and 21.4±3.7, respectively, at 5 min). However, only smoked cocaine caused significant % increases in Raw (39.5 ± 14.2), in contrast to nonsignificant % changes after IV cocaine (11.7 ± 13.2) and smoked "placebo" (17.6 ± 11.8). IV cocaine had no significant effect on % change from baseline in PAP (3.7±6.5) or PVR (-10.5±7.1). We conclude that 1) smoked cocaine base, but not IV cocaine HCl, causes acute bronchoconstriction that is probably mediated by topical airway irritation and could account for reports of crack-induced wheezing and asthma attacks; and 2) cocaine does not acutely constrict the pulmonary vascular bed, arguing against cocaine-induced pulmonary vasoconstriction as a mechanism of crack-related lung diffusion impairment. **ACKNOWLEDGEMENT:** Supported by NIDA Grant # RO1 DA08254.

MORPHINE'S IMMUNOSUPPRESSIVE EFFECTS FOLLOWING CHRONIC ADMINISTRATION

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Although it is generally assumed that morphine's immunosuppressive effects attenuate with chronic morphine exposure, the development of tolerance to these suppressive effects has not been examined extensively. This study investigates the effects of chronic morphine administration on several measures of immune function including natural killer (NK) cell activity, Con-A and PHA induced splenic T-cell proliferation, and LPS stimulated splenic B-cell proliferation. Groups of Lewis rats received either tap water or 0.2, 0.4, or 0.6 mg/ml morphine sulfate in their drinking water. After three weeks of drinking tap water or morphine water, both groups received a subcutaneous injection of saline or 15 mg/kg morphine sulfate one hour before sacrifice for immune testing. In the water drinking group, the acute morphine injection significantly suppressed NK cell activity and mitogen stimulated splenocoyte T- and B-cell proliferation. A single injection of 15 mg/kg morphine also suppressed the mitogen stimulated splenic T-cell proliferation and splenic B-cell proliferation in the morphine drinking rats; however, the morphine induced suppression of NK cell activity was attenuated in animals that rank morphine water. Tolerance to morphine induced antinociception in a hot water tail withdrawal assay was also demonstrated in separate groups of rats that drank water with 0.2, 0.4, or 0.6 mg/ml morphine for three weeks. In addition, withdrawal induced weight loss was observed in rats that drank water with 0.2 and 0.6 mg/ml morphine sulfate. These results suggest that rats develop tolerance to some but not all of morphine's immunosuppressive effects following chronic exposure to the drug.

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CREATINE KINASE ELEVATION IN COCAINE USERS

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Background: Rhabdomyolysis is a serious complication of cocaine abuse, frequently leading to renal failure and death.

Objective: The purpose of this study was to assess the incidence of creatine kinase (CK) elevation in cocaine users and evaluate other contributing factors.

Design/Method: Using the hospital's computerized registry of emergency room visits and discharges during a one year period all patients with positive cocaine urine toxicology and elevated CK values were identified. The charts of patients with CK over 500 I.U. were reviewed retrospectively.

Results: CK above 500 IU were noted in 213 (151 patients) out of 4094 cocaine positive urine tests (1366 patients). There were 125 men and 26 women aged 16-73 years (mean 39.9). Route of administration was "crack" in 77, intravenous in 42, intranasal insufflation in 33 and unknown in 14 patients. Alcoholism was reported by 77 and intravenous drug use by 52 patients. Thirty seven patients were HIV+; seven of them were on AZT. Single seizures were noted in 8 patients. Agitation was present in 35 and delirium in 32 patients. CK elevation over 2000 IU was noted in 24 patients but only 4 of them developed renal failure. In 37 patients (24.5%) no other risk factor for rhabdomyolysis could be identified.

Conclusions: Cocaine users treated at an inner city hospital frequently have elevated CK values. Possible contributing risk factors include use of alcohol or heroin and agitation. All patients who were HIV+ or on AZT had a return of CK levels to normal after the acute intoxication. In patients without other risk factors cocaine can be the only cause of rhabdomyolysis because of vasoconstriction or direct muscle toxicity.

EFFECT OF MORPHINE ON CELL COMPOSITION AND SURFACE MARKER EXPRESSION IN THE MOUSE PERITONEAL CAVITY.

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Previous studies from our laboratory have shown that the immunosuppressive effect of the sc implantation of 75 mg morphine (M) pellets in C3HeB/FeJ mice is due in part to a reduction of macrophage (Mϕ) function in the spleen. Recently, we reported that morphine pellet implantation in mice resulted in reduced Mϕ numbers in the spleen 48 hr later, suggesting that reduction of Mϕ numbers may be an important mechanism in the immunosuppression seen in morphine pellet-implanted mice. In this study we show using flow cytometry that, in contrast to what we have observed in the spleen, morphine-pelleted mice have 32% more Mϕ in their peritoneal cavity (PC) than placebo-pelleted controls, as assessed by staining for the Mϕ surface marker F4/80. Similarly, morphine-pellet implantation increased the % Mac-1 positive cells by 30% in the PC. Both effects are blocked by the simultaneous implantation of a naltrexone pellet. Morphine pellet implantation did not significantly reduce sIg^+ B cells numbers in the PC, but did result in a reduction in both the number (44%) of MHC Class II+ cells (mostly B cells) and the level of expression (50%) in the PC. Thus, while morphine pellet implantation does not alter the total cell numbers in the PC of the mice, it changes the cell composition and the level of surface marker expression.

REFERENCES: Available from first author upon request.

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ACUTE ACTIVATION OF CIRCULATING PMNS FOLLOWING *IN VIVO* ADMINISTRATION OF COCAINE: A POTENTIAL ETIOLOGY FOR PULMONARY INJURY

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Crack cocaine has become a major drug of abuse in the United States, and its use is associated with a broad spectrum of pulmonary complications. The present study was conducted to determine whether controlled *in vivo* administration of cocaine (inhaled or intravenous) alters the function of circulating inflammatory cells in a manner capable of contributing to acute lung injury. Subjects that regularly smoked crack cocaine were asked to abstain from illicit drug use for at least 8 hours, and were then administered one of the following treatments on each of 4 study days: inhaled cocaine base (45 mg), inhaled placebo (4.5 mg cocaine base, a subphysiologic dose), intravenous cocaine HCl (0.35-0.50 mg/kg) or intravenous placebo (saline). Samples of blood were obtained from blood cells isolated before and 10-45 minutes after treatment. The administration of either cocaine base or cocaine HCl, but not their corresponding placebos, resulted in the activation of circulating polymorphonuclear neutrophils (PMNs). Exposure to cocaine *in vivo* enhanced the antibacterial activity of PMNs, and antitumor activity also increased following acute administration of cocaine. Finally, acute exposure to cocaine enhanced production of interleukin 8 (IL-8), a potent PMN chemo-attractant and neutrophil-activating factor associated with both acute and chronic lung injury. These studies demonstrate that acute *in vivo* exposure to cocaine activates the effector function and cytokine production of circulating PMNs. Therefore, it is possible that repeated bursts of acute inflammatory activity resulting from repeated crack use could contribute to lung injury.

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THE EFFECT OF DELTA-9-THC ON FRONTAL CORTICAL-BASAL GANGLIA SYSTEM DURING LOCOMOTOR AND LEARNING TASKS

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The aversive effect of marihuana on human including disruption of locomotor, learning and memory abilities. Considerable density of cannabinoid receptors were found, among other areas, in the frontal cortical-basal ganglia system. This system is also involved in many locomotor and cognitive functions. The present study using multiple channel, single unit recording technique to examine the effect of Δ^{-9}-Tetrahydrocannabinol (Δ^{-9}- THC) on neuronal activities in medial frontal cortex (mPFC), striatum (STR) and substantia nigra pars reticulata (SNr) during the delayed match to sample (DMTS) and reaction time tasks (RT). Six arrays of eight stainless steel microwires were implanted bilaterally in mPFC, STR and SNr after successful training. Single and ensemble neuronal activities were analyzed by using peri-event histogram, joint peri-stimulation histogram (JPSH) and discrimination analysis. Delta^{-9}-THC at dose of 0.5-1.0 mg/kg (i.p.) increased the error responses in both tasks comparing to the control condition. In DMTS task, the neuronal spike activities associated with sample, delay and match events were observed in all three recording areas. A corresponding changes in neuronal presentation of sample, delay and match episodes were detected after Δ^{-9}-THC treatment. Delta^{-9}-THC also alter the correlation patterns between mPFC and STR neurons revealed by JPSH around sample and match events. In RT task, the sensory and motor related neuronal responses were interrupted by Δ^{-9}-THC. The data suggests that frontal cortical basal ganglia system is part of neuronal circuitry through which cannabinoid exert its effect on the locomotor, learning and memory process. Supported by DA2338

THE BLUNTED RESPONSE OF T-BLASTS TO IL-2 AND REDUCED NEUROTRANSMITTERS IN PRENATAL-ETOH-EXPOSED MICE

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Evidence from humans, non-human primates and rodents supports our hypothesis that *in utero* ethanol exposure alters immune system function. Very few studies, however, involve long-term observations on the immune function of the offspring exposed to ethanol in utero. To fill this void, examine the possible relationship between the changes in **T cell function** and the concentrations of peripheral **neurotransmitters (Norepinephrine NE and serotonin 5-HT)** in 15-mo-old C57BL/6 mice exposed to ethanol **in utero.** Ethanol(EtOH) was administered orally to pregnant mice in a chocolate-flavored liquid diet, The control groups were fed an isocaloric sucrose diet in volumes equal to the mean volume consumed by the EtOH-diet group, or fed laboratory chow ad libitum (N = 7 per group). The duration of the diet exposure was gestation days 5-18. The animals were sacrificed at 15-month and the spleens were removed for assessment of T cell function (response of T-blasts to IL-2) and for the measurement of NE and 5-HT concentrations by HPLC. The data were subjected to Analyses of Variance (ANOVA), and the litter was considered the unit of analysis. Prenatal ethanol exposure reduced the proliferative response of Con-A stimulated T blasts when cultured with IL-2. Although the basic counts(CPM/min) of the T-blasts in the EtOH-treated group was higher than control groups in the absence of IL-2, they were less responsive to the presence of IL-2. Thus, the stimulation index (IL-2/B) for cells obtained from the prenatal ethanol group was significantly lower (P=0.002) than controls even in the middle-aged offspring. The concentrations of NE and 5-HT (ng/mg protein) in the spleens from prenatal ethanol mice showed remarkable decreases as compared to control animals. The level of 5-HT, although lower, did not reach significance because of greater variance among samples. The correlation coefficient of NE (r=0.698) or 5-HT (r=0.767) with IL-2/B accounted for 49% and 59% of IL-2/B variance respectively. The regression analysis indicated significant correlation between concentrations of NE ($p<0.02$) and 5-HT ($P<0.02$) with the stimulation index (IL-2/B) of the T-blast response to IL-2. Our data indicate that prenatal ethanol exposure has a long-term influence on the function of T lymphocyte function. The reduction of periperal neurotransmitters (NE and 5-HT) produced by prenatal ethanol exposure may play an important role in the altered immune function of mice. (The study was partially supported by AA 06611)

RETAIL MARIJUANA MARKETS IN NEW YORK CITY

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The techniques by which marijuana is bought and sold at the retail level has been neglected in the field of drug research. Through analysis of ethnographic data, this paper will briefly explore the historical evolution of retail marijuana markets in New York City. Older types of retail markets, such as street and park markets, are constantly being replaced by newer more innovative modes of retail sale, such as delivery services and storefronts. A working typology of these marijuana markets is proposed: street and park markets, delivery services, private networks of distribution, and storefronts. The most popular marketing strategy for marijuana sales in the mid 1990s involve storefronts--seemingly legitimate businesses like newsstands, record shops, boutiques, and video rental outlets-- but whose main income is derived from sales of marijuana. Storefronts and delivery services seem to have effectively separated themselves from the more prominent hard drug (i.e., crack-cocaine, powdered cocaine, and heroin) markets which exist in the same inner-city neighborhoods. The reasons why marijuana storefronts are tolerated to some extent by law enforcement may include: 1) the role of storefronts in keeping marijuana dealing in an indoor location, and off the streets, 2) the absence of hard drug sales at these locations, and 3) the attempts storefronts make in maintaining the facade and actual operations of a legitimate business. Implications regarding possible effects of these market shifts on use patterns and prevalence, and appropriate policy responses will be discussed.

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FLUOXETINE VS PLACEBO IN DEPRESSED ALCOHOLIC SUBSTANCE ABUSERS

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Our own recent clinical trials have suggested efficacy for the selective serotonin agonist fluoxetine in treating the alcohol use and depressive symptoms of alcoholics with comorbid major depression (MDD) and depressive symptoms (Cornelius *et al.,* 1995). However, to date, the efficacy of selective serotonin agonists such as fluoxetine in the treatment of substance abusing patients with comorbid MDD remains unclear. We now report preliminary data from two randomized double-blind substudies of fluoxetine versus placebo in 14 patients with MDD, alcoholism, and marijuana abuse; and in 9 patients with MDD, alcoholism and cocaine abuse (AA09127). Cumulative marijuana use during the 12 week course of the study was four-fold higher in the placebo group than the fluoxetine group (X=15.8 vs 3.8 joints, F=6.45; df=1,9; p=0.032), which was a significant difference. Cumulative cocaine use was eight-fold higher in the placebo group than the fluoxetine group (X=18.5 vs 2.2 hits), though this difference was not significant in the small subsample (N=9). These findings suggest efficacy for fluoxetine in treating the marijuana use and the cocaine use of substance abusing patients with comorbid major depression. Further studies with larger sample sizes will be needed to make a more definitive conclusion concerning efficacy in these patient populations.

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THE ACTIVITY OF NEW NICOTINIC ANALOGS AT THE $\alpha_4\beta_2$ RECEPTOR SUBTYPE.

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The predominant nicotinic acetylcholine receptor (nAChR) subtype found in mamalian brain is $\alpha_4\beta_2$ which therefore, may underlie several of the pharmacological effects of (-)-nicotine. The objective of this study was to identify the effects of nicotine mediated by, this receptor subtype. Several novel nicotinic analogs were evaluated for receptor affinity (^{3}H-nicotme binding), pharmacological potency (antinociception and locomotor activity) and current induction in *Xenopus* oocytes transfected with the $\alpha_4\beta_2$ subunits. Our results indicate that the analogs fall into one of three general categories: those similar to (-)-nicotine, such as epibatidine and isonicotine, which bind well to nAChRs, have their behavioral effects blocked by the nicotinic antagonist, mecamylamine and generate currents in oocytes injected $\alpha_4\beta_2$ mRNA; secondly those, such as lobeline and N-ethyl-N-norisonicotine, which bind well, are not blocked by mecamylamine and do not illicit currents; and finally those, such as the bridged nicotine analogs and N-cyclopropylmethyl-N-nornicotine, which do not bind, yet produce behavioral effects insensitive to mecamylamine and do not induce currents in oocytes. These results suggest that binding affinity and sensitivity to mecamylamine are corequisites to $\alpha_4\beta_2$ receptor subtype activation while agonists with different profiles may associate with other nicotinic receptor subtypes.

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COTININE PHARMACOLOGY: BRAIN UPTAKE AND METABOLISM, EFFECTS ON DOPAMINE RELEASE AND LACK OF BEHAVIORAL SENSITIZATION AFTER CHRONIC ADMINISTRATION TO RATS

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Cotinine (COT) is a major peripheral metabolite of nicotine (NIC), and COT has recently been shown to be the most abundant metabolite in brain after peripheral NIC administration to rats (Crooks *et al.,* 1995). Other NIC metabolites in brain detected in our subsequent studies included nornicotine and norcotinine (Crooks *et al.,* 1996). When administered to humans, COT has been reported to diminish the craving for tobacco (Keenan *et al.,* 1994). The hypotheses to be tested are that COT passess the blood-brain barrier from the periphery, accumulates and is metabolized in brain, enhances dopamine (DA) release and/or inhibits DA uptake from brain slices, and produces behavioral sensitization. [^{3}H]COT was administered s.c., and COT brain levels determined over 18 hrs. COT was detected at 5 min, peaked at 30-60 min (0.15% of dose), and at 18 hrs was still present in brain. No metabolism of COT was detected in brain over the entire time course. In other studies, COT (0.1 μM - 3 mM) evoked [^{3}H]DA release from superfused rat striatal slices in a concentration-dependent manner with an EC50 of 30μM. However, over the same concentration range, COT did not inhibit [^{3}H]DA uptake into striatal synaptosomes. In locomotor activity studies, COT (0.3-10 mg/kg, s.c., 8 injections, once every 48 hrs) did not produce behavioral sensitization, as did administration of NIC (1 mg/kg). Thus, COT passess the blood-brain barrier from the periphery; however, it is not metabolized in brain, in contrast to its extensive metabolism in the periphery. Further, COT enhances DA release from dopaminergic presynaptic terminals, however, behavioral sensitization was not observed. Thus, although COT's neurochemical effects are similar to NIC's, its behavioral pharmacology is different from that of NIC.

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BEHAVIORAL STUDIES EXAMINING THE EFFECTS OF CHRONIC NICOTINE EXPOSURE IN RATS

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Chronic exposure to nicotine (NIC), a heavily abused licit drug, may result in either tolerance or sensitization to a variety of behavioral effects, and subsequent dependence can result as revealed by an abstinence syndrome when subjects are withdrawn from NIC. To better understand the behavioral changes caused by chronic NIC exposure, the effects of chronic NIC exposure were examined upon (1) schedule-controlled behavior and (2) locomotor activity in male Sprague-Dawley rats. Rats received two subcutaneous injections daily of either NIC or saline (control group) administered 9 h apart. NIC was administered in doses of 0.6 and 1.2 mg/kg. The first injection was given 20-min prior to a 60-min session during which rats worked under a VI 3 min or FI 3 min schedule of food reinforcement. Locomotor activity measurements were performed over a 60 min period immediately after the second injection of NIC. After subchronic (7 days) and chronic (29 days) of NIC exposure rats developed sensitization to the rate-increasing effects on schedule-controlled behavior and locomotor activity. Substitution of saline for NIC following both periods of nicotine treatment resulted in decreases in activity to baseline levels observed in saline-treated controls. The present results suggest that a regimen of two daily injections of 0.6 and 1.2 mg/kg for 7 and 29 days does not appear to produce either tolerance or physical dependence. The possibility exists that evidence of tolerance development or an abstinence syndrome might be observed with either different strains or with different routes and frequency of nicotine treatment.

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ENHANCED RATE-INCREASING EFFECTS OF NICOTINE AND CAFFEINE ON SCHEDULE-CONTROLLED BEHAVIOR WHEN GIVEN IN COMBINATION

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Lever pressing responses of squirrel monkeys produced either brief 5 mA electric shocks under a 3-min fixed-interval (FI) schedule or food-pellet deliveries under a 5-min FI, 30 response fixed-ratio (FR), multiple schedule. Injection of 0.1 to 1 mg/kg of nicotine i.m. or 3 to 30 mg/kg of caffeine increased FI responding maintained by food or shock delivery by 25% or more but had little effect on FR responding maintained by food. When nicotine was given in combination with 3 to 30 mg/kg of caffeine, much larger increases in FI responding maintained by food or shock delivery occurred and patterns of responding were disrupted; increases in responding approximated the additive effects of the single nicotine or caffeine injections or the maximal effects produced by cocaine or d-amphetamine injections under the same conditions. These findings demonstrate a marked enhancement of the rate-increasing effects of nicotine and caffeine on schedule-controlled behavior when they are given in combination which appears relatively independent of the events maintaining responding.

IN VIVO DESENSITIZATION OF NICOTINE'S ANTINOCICEPTIVE EFFECT IN MICE

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Desensitization to nicotine's effects is believed to play an important role in the development and maintenance of dependence to this drug. The objective of this study was to investigate and characterize the development of *in vivo* desensitization to nicotine's antinociceptive effect after intrathecal (i.t.) injection. Male ICR mice were pretreated i.t. with different doses of nicotine at different times prior to a second i.t. injection of nicotine (20 µg/mouse) and the effect on the tail flick response was measured. In mice pretreated i.t. with 1 µg nicotine/animal and then challenged at different times with nicotine, *in vivo* desensitization to nicotine occurred very rapidly after injection (10 min) and lasted for 2 hrs. Desensitization was blocked by mecamylamine, a nicotinic antagonist, suggesting the involvement of nicotinic receptors in this process. Cross-desensitization to nicotine was investigated by pretreating mice with different nicotinic ligands and then challenged them with nicotine. Ligands which are mecamylamine-sensitive after i.t. injection such as (+)-nicotine, nor-nicotine and ABT-418 showed cross-desensitization to nicotine in this model. However, ligands which are mecamylamine-insensitive such as N-methylcarbamylcholine, DMPP, lobeline, (+)-bridge-nicotine analog and acetylcholine did not develop cross-desensitization to nicotine. Interestingly, desensitization did not develop to these compounds by themselves. These results suggest that multiple mechanisms are involved in the cholinergic desenstization of spinal nicotinic responses in mice.

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EFFECTS OF INTRAVENOUS AND SMOKED NICOTINE ON PUPIL SIZE AND PUPILLARY LIGHT REFLEX.

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It has been reported that intravenous administration of nicotine causes brief pupillary dilation followed by pupillary constriction, Pupillary dilation has been attributed to stimulation of sympathetic ganglia and the release of catecholamines; whereas, the miosis may be due to acetylcholine release on pupillary smooth muscle or stimulation of parasympathetic ganglia. The purpose of the present study was to compare the pupillary effects of rapidly administered nicotine after smoking and intravenous administration in overnight, cigarette-deprived volunteers, Six subjects were given 0, 0.75, 1.5 and 3.0 mg of nicotine by both smoked and intravenous routes of administration. Pupillary size and components of the light reflex were measured before (baseline) and from 2 to 120 min after drug administration. Pupillary responses were made with a dynamic pupillometer and Polaroid photographs. The pupillometer averaged the initial pupillary diameter, constriction velocity, constriction amplitude and dilation velocity from 4 flashes of light. Baseline averages were: diameter 5.1 mm; constriction velocity 3.4 mm/sec; and amplitude of constriction 0.9 mm. At the time-points measured, neither smoked nor intravenous nicotine had significant effects on pupil size or measures of the light reflex. If nicotine causes pupillary changes, they must occur during or immediately after administration making pupillary effects more transient than EEG and performance effects.

NICOTINE DISCRIMINATION IN NONSMOKERS VERSUS SMOKERS

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Smokers have been shown to discriminate nicotine alone, isolated from tobacco smoke and delivered by nasal spray. We examined differences in nicotine discrimination between nonsmokers and smokers; attenuated discrimination in smokers would suggest development of tolerance to discriminative stimulus effects of nicotine, while superior discrimination in smokers would suggest that past experience with nicotine is important in being able to discriminate the drug. Male and female nonsmokers (n=8) and smokers (n=10) were trained to discriminate 20 ug/kg by nasal spray from placebo (0) on Day 1. On Day 2, both groups were tested on generalization of this discrimination across 0, 3, 6, 12, and 20 ug/kg, administered in random order (@25 mins). A quantitative behavioral discrimination task, used in previous research, was employed. On Day 3, subjects were instructed to self-administer sprays from the 20 ug/kg vs. 0 bottle in a forced-choice procedure. All but one smoker learned to reliably discriminate 20 ug/kg nicotine from placebo (≥ 80% correct) on Day 1. Nicotine-appropriate responding on Day 2 was significantly attenuated in smokers vs. nonsmokers at 20 ug/kg (67% vs. 95%, resp.), and the dose-response curve was flatter for smokers vs. nonsmokers, both suggesting tolerance. There was no difference in responding at other doses. Smokers also showed attenuated responses on the subjective measure of "buzzed", which was associated with discrimination responding. Nicotine self-administration was significantly greater in smokers vs. nonsmokers, as expected, but was not related to discrimination behavior. Self-administration was also less in female vs. mate smokers. These results indicate that smokers may become tolerant to the discriminative stimulus effects of nicotine, perhaps promoting increased use.

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CIGARETTE SMOKING IN METHADONE MAINTENANCE TREATMENT PATIENTS: RACE AND GENDER DIFFERENCES

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The purpose of this study was to assess smoking habits and attitudes in methadone maintenance treatment (MMT) patients and to explore racial and gender differences. Outpatient MMT patients completed a smoking history questionnaire to assess a range of smoking variables and provided expired breath carbon monoxide (CO) and urine samples (for cotinine analysis) to obtain physiological indices of smoking. Of 179 patients surveyed, 92% (n=165) were current smokers, 6% (n=11) were former smokers, and 2% (n=3) were never smokers. The mean age of subjects was 38.7 yrs. Subjects smoked a mean of 24.8 (SD=12.3) cigarettes per day, first initiated smoking at age 13.6 yrs (SD=4.2) and had smoked for an average of 22.2 yrs (SD=7.2). The mean score on the Fagerstrom Tolerance Questionnaire (FTQ) was 7.5 (SD=1.8), indicating an overall high degree of nicotine dependence. The mean baseline CO reading was 20.3 ppm (SD=9.6) and the mean urinary cotinine level was 1597 ng/ml (SD=937). Sixty-one % (n=101) of subjects expressed interest in quitting within six months. preliminary analysis of race and gender differences indicated that black subjects (M=21.6) smoked significantly fewer cigarettes than white subjects (M=27.5) and had lower baseline expired breath CO readings (M=18.8 vs. 21.6 ppm). Females scored significantly higher than males on the FTQ and on a measure of health risk perception, but scored lower than mates on quitting self-efficacy. Overall, these results indicate high rates of smoking in the MMT population, confirm prior findings of racial differences in smoking habits, and suggest that many MMT patients are interested in quitting, but that females may have more difficulty quitting than males due to greater dependence and lower self-efficacy.

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CAN CIGARETTE SMOKING IN YOUNG WOMEN BE PREVENTED BY ENHANCED SPIRITUALITY?

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This paper presents further analysis of a longitudinal field study that followed 54 late adolescent and young adult females (mean age=18.5 years) for eight months. Substance use (cigarettes and alcohol), stressors, and personality variables were measured initially (T1), after five months (T2), and after eight months (T3). An initial analysis of this data showed stress regarding physical appearance to be a risk factor for cigarette smoking, and led to the recommendation that smoking prevention programs for young women focus on body image and the drive to be thin. This report raised several issues. 1) Is stress concerning physical appearance specifically related to cigarette smoking or a generic source of anxiety also related to alcohol consumption? 2) Self-confidence was a risk factor rather than a protective factor. Thus, no preventive psychological factors had been identified. Might spirituality be such a factor, given previous research establishing its stress-inoculating effects? This analysis produced two conclusions. 1) Stress concerning physical appearance is specifically related to cigarette smoking (r= .222; p= .035), and not to alcohol consumption (r= -.039; p= .715). Alcohol consumption is related to relaxation (r= .324; p= .002), while cigarette smoking is not (r=.035; p= .741). 2) Spirituality is a positive psychological resource which helps to prevent cigarette smoking. Multiple regression analysis, controlling for cigarette smoking at T1, with cigarette smoking at T3 as dependent variable, identified predictive factors. The final model contained two main effects: cigarette smoking at T1 (Beta=.625; p=.000), and an interactive variable containing family and friends who smoke, current alcohol usage, self-confidence, hostility, stress concerning physical appearance, and spirituality (Beta=.329; p=.001). The model had high predictive value (Multiple R=.903; Multiple R-SQ=.815; F-ratio=105.974; p-value=.000). Spirituality was the only factor in this model that led to reductions in cigarette use. The effect size was small, but suggests that personally-meaningful spirituality can be a health resource when it has been developed.

TREATMENT WITH NORTRIPTYLINE AND POST-QUIT MOOD CHANGES IN SMOKERS WITH AND WITHOUT DEPRESSIVE HISTORIES

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Negative mood is associated with smoking cessation outcome. Poor mood at the beginning of treatment and increases in negative mood immediately after quitting are also related to smoking cessation failure. The present study examined the effect of nortriptyline and two psychological group treatments on post-quit mood changes in subjects with and without a history of major depressive disorder (MDD). Findings are based on 199 subjects, 33% reported a history of MDD. 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. Nortriptyline treatment took place during weeks 1-12. Psychological treatment began at week four, and continued for eight weeks. The quit date was week five. Mood was assessed using the Beck Depression Inventory (BDI), Profile of Mood States (POMS), and Shiffman Withdrawal Scale, at baseline and post-quit (3, 5, & 8 days following the quit date). Analyses indicate a significant effect for nortriptyline on mood changes from baseline to 3, 5, and 8 days post-quit. Five of six POMS subscale scores declined more, or increased less, for subjects taking nortriptyline than those taking placebo. A significant interaction was also found for drug assignment by MDD history, with the MDD positive + nortriptyline group reporting a greater decrease in depressive symptomology and fatigue from baseline to day eight than the other groups. Subjects in the mood management intervention experienced less negative affect at day three but not later days. These findings suggest that nortriptyline and mood management counseling may be effective in preventing increases in negative mood states following quitting.

THE EFFECT OF VENLAFAXINE ON SMOKING CESSATION IN SUBJECTS WITH AND WITHOUT A HISTORY OF DEPRESSION

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Recent studies have indicated that the use of antidepressants may be an effective intervention to help smokers in their attempt to quit. Our review of the extant studies and the neurophysiology of nicotine activity suggested that antidepressants with noradrenergic activity would be most likely to be effective. At the same time, we were interested in using a medication that would be easily used by physicians and well-tolerated by patients. Venlafaxine is a novel antidepressant with both noradrenergic and serotonergic reuptake properties but without significant anticholinergic activity. It is easily administered by physicians in that it does not require monitoring of blood levels. Its side-effect profile is similar to that of the selective serotonin reuptake inhibitors (SSRIs), and it has been reportedly well-tolerated by most patients. In a randomized, double-blind, placebo controlled pilot trial of venlafaxine as an adjunct to smoking cessation treatment, venlafaxine appeared to be inferior to placebo in facilitating three consecutive weeks of abstinence. Point prevalence abstinence rates of the placebo versus venlafaxine group at eight weeks did not differ. Half of the subjects assigned to venlafaxine experienced notably aversive side effects. Of these, two remained in the study unmedicated, five withdrew from the study, and three attempted to wait out moderate but bothersome side effects for several weeks. Despite random assignment to medication group, women were assigned to active medication with significantly greater frequency than were men (71% vs. 37%). Women on active medication were somewhat more likely than men to report severe side effects (42% versus 14%). REFERENCES: Available from Dr. Frederick upon request. ACKNOWLEDGEMENTS.: Supported by NIDA grants DA-09253 and DA-02538

HEAVY AND LIGHT SMOKERS ASSOCIATE THE WORD "CRAVING" WITH DIFFERENT STATES

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"CRAVING' is an elusive concept. The state with which it is associated may depend on the salient characteristics of the abused substance, the heaviness of use, and level of abstinence. For example, we have prior data showing that while cocaine users associate "CRAVING" with seeking the drug high, opiate users associate it with reducing drug withdrawal. This study examined whether heaviness of use and treatment status influence how frequently smokers of nicotine, a drug with a clinically significant withdrawal syndrome: Use "CRAVING" to describe feelings of wanting to smoke; Use "CRAVING" to describe feelings of "high", or wanting "to get rid of bad moods", "to get rid of withdrawal", "to boost pleasure from nonsmoking activities"; Acknowledge feelings associated with "CRAVING" during abstinence. Results showed that heavy smokers not in treatment (N==48) use "CRAVING" to describe feelings of wanting to smoke, and acknowledge feelings of "CRAVING" during abstinence more frequently than light smokers (N=20), and than heavy smokers in treatment (N=55). Independent of treatment status, heavy smokers associate "CRAVING" with reducing withdrawal, and light smokers with boosting pleasure. These results imply that in heavy smokers, anti-"CRAVING" treatments should provide withdrawal-relief in order to be maximally effective. Furthermore, the frequency of nicotine-craving may be underestimated among heavy users in treatment due to their reluctance to label feelings of wanting to smoke with the word "CRAVING".
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SMOKING CESSATION INTERVENTIONS FOR SUBSTANCE ABUSERS

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This study investigated whether alchoholics/drug addicts enrolled in outpatient substance abuse treatment would stop smoking when advised by a physician to quit, and whether their quit rates would increase when that advice was linked to adverse health effects from smoking. Subjects (N=98) in this randomized trial were male veterans at the SFVAMC. Most were Caucasian (46%) or African American (43%), unemployed (37%), average age of 46.4 years, and had 13.4 years of education. Alcohol was the most frequent primary drug problem (37%), followed by cocaine or crack (27%) and heroin (22%). At baseline, cigarettes averaged 20.6 per day and mean CO level was 23.6. No differences on demographic or smoking measures were found between the two treatment groups. Assessments of smoking status were taken at 1, 3, 6, and 12 months following the advice session. No significant differences between groups were found. Even comprehensive advice to stop smoking appears ineffective in assisting smoking cessation in this population. Decreases, however, in the number of cigarettes self-reported ($p.<01$) and in measured CO levels ($p=.06$) were found across treatment groups. This may be the result of more "successful" subjects returning for follow-up assessments. The majority of subjects reported remembering receiving advice to quit smoking and a statistically greater proportion of subjects in the "Linked" condition reported remembering the advice from the 3-month follow-up onwards. Most subjects in the "Linked" condition remembered each aspect of the advice session (H&P), X-ray, PFTs, Lab Work, EKG, CO, Plastic Models, Quit Date, Smoking Cessation Manual, Dining Guide, & Tip Sheet). The CO was recalled least frequently and the Dining Guide was deemed least helpful.

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DOPAMINERGIC MECHANISMS IN THE DISCRIMINATIVE STIMULUS EFFECT OF NICOTINE

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Substantial evidence has accumulated to support nicotine as a reinforcer in humans and laboratory animals. Like most drug reinforcers, nicotine increases the extracellular concentration of dopamine in the nucleus accumbens, a key structure in the mesocorticolimbic reward pathway. Nicotine also produces a robust discriminative stimulus in animals. Although this stimulus has generally been shown to be specific to nicotinic agonists, some studies have implicated increased dopaminergic activity as a mediator of nicotine's discriminative effect, while other studies suggest that dopaminergic manipulations have only a minor influence. The present study examined the effects of dopaminergic agonists with various mechanisms of action in rats trained to discriminate injections of 0.4 mg/kg nicotine from saline in a two-lever procedure of food-reinforced lever pressing. The dopamine releasing agent &amphetamine and reuptake inhibitor cocaine produced partial substitution for the nicotine stimulus, but the D2 agonist bromocriptine and dopamine autoreceptor antagonist (+)-AJ-76 produced little nicotine-like effect when administered up to doses which reduced overall response rates. Doses of d-amphetamine producing maximal substitution were then administered in combination with the D1/D2 antagonist haloperidol. The results indicated only partial attenuation of amphetamine's nicotine-like stimulus effect. Overall, these data suggest that only some forms of dopaminergic stimulation produce substantial nicotine-like effects in the drug discrimination procedure, and that activity at other systems may play a role in the nicotine-like effects of nonselective dopamine agonists.

AMBIENT AND OUTDOOR CARBON MONOXIDE LEVELS AMONG NON-SMOKERS IN LOS ANGELES

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As part of a programmatic study of contingency management procedures for smoking cessation, we recognized a need for an empirically derived criterion using carbon monoxide (CO) to indicate abstinence from tobacco smoking. It is known that environmental sources of CO may affect CO contained in breath, especially in a polluted city such as Los Angeles. We collected breath samples from 76 non-smokers at two locations: staff inside a methadone clinic and passersby at a park near a busy freeway. Results indicated that CO levels drawn from staff at the indoor location (M=3.97 parts per million, SD=0.68) were significantly higher and more stable than those drawn from passersby outdoors (M=3.16 ppm, SD=.64; $t(74)=2.84$, $p<.01$). The distribution of CO levels for the outdoor group indicated that 95% of non-smokers expressed six or fewer parts per million of CO in their breath samples. Application of these findings will be made to an ongoing contingency management trial for smoking cessation and may be useful to other studies using CO as an indicator for smoking status.

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MECHANISM OF PHENCYCLIDINE BINDING IN HAIR

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The mechanism of phencyclidine (PCP) binding to pigmented and nonpigmented hair of Long-Evans (LE) rats was investigated. PCP was given by ip injection to LE rats daily for five days and pigmented and nonpigmented hair was collected 14 days later and analyzed for PCP by GC/ion trap mass spectrometry. PCP concentrations in pigmented hair were 2.86±0.55, 10.3±1.15, 14.33±1.43, and 29.2±6.02 ng/mg of hair after doses of 1, 4, 12, and 24 mg/kg, respectively; PCP concentrations in nonpigmented hair were 0.3±0.07, 0.47±0.04 and 1.05±0.39 after 4, 12, and 24 mg/kg, respectively. PCP was not detected in nonpigmented hair after a dose of 1 mg/kg daily for five days. Pigmented hair from previously dosed animals was pooled and washed daily for ten days with either deionized water or 200 mM phosphate buffer, pH 10.5. Hair aliquots were obtained daily from these protocols and analyzed in triplicate for PCP. PCP concentrations for non-washed, pigmented hair were 14.91±0.98 ng/mg of hair. No significant differences were seen when daily aliquots of water-washed hair were analyzed and compared to the non-washed hair. In buffer-washed hair, PCP concentrations decreased by 80%. This study demonstrates that PCP is incorporated into pigmented and nonpigmented hair in a dose proportional manner with a 30 fold preference for pigmented hair. Decreasing the percentage of ionized PCP appears to significantly change the nature of PCP binding in hair.

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LACK OF PCP-LIKE EFFECTS OF ARGIOTOXIN-636, A POLYAMINE TOXIN NMDA RECEPTOR ANTAGONIST

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Polyamines derived from spider toxins are unique noncompetitive open - channel blockers that inhibit the binding of [^{3}H]MK-801 at concentrations approximately 100 to 10,000-fold higher than those which antagonize NMDA receptor function. These results and other *in vitro* data support the conclusion that polyamine toxins antagonize the NMDA receptor-ionophore complex by a novel mechanism. The purpose of this study was to determine whether this unique *in vitro* activity translates into a unique pharmacological profile *in vivo* A drug discrimination procedure in rats was used to determine whether the polyamine argiotoxin-636 would produce PCP-like effects typical of high affinity open-channel blockers such as MK-801. Rats were trained to discriminate PCP (2 mg/kg, *i.p.*) from saline under a 2-lever fixed-ratio 32 schedule of food reinforcement. Tests were conducted with PCP (0.5 - 8 mg/kg, i.p.), MK-801 (0.02 - 0.3 mg/kg, i.p.) and argiotoxin-636 (1 - 30 mg/kg, *i.p.*). MK-801 fully substituted for PCP at doses of 0.075 and 0.15 mg/kg. argiotoxin-636 completely failed to substitute for PCP, although the highest dose decreased rates of responding providing evidence for CNS activity. These results provide further evidence that it should be possible to develop clinically useful NMDA antagonists without PCP-like side effects and abuse liability.

PHENCYCLIDINE CAUSES TIME-DEPENDENT REGULATION OF RAT CYP2C11 FUNCTION, EXPRESSION AND mRNA

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These studies determined the effects of chronic phencyclidine (PCP) treatment on cytochrome P_{450} 2C11 (CYP2C11) function, expression and mRNA levels. Male Sprague-Dawley rats received 1, 3, 10 or 20 day PCP infusions at 18 mg/kg/day by s. c. minipumps. Control animals received saline infusions for 3 or 20 days (n=4 per group). Livers were collected 24 post infusion, when PCP was completely cleared from the animals. In microsomes prepared after one or three PCP infusions, CPY2C11 function (as measured by 2α-OH testosterone metabolism) decreased significantly to 46 ± 18% and 28 ± 18% of control values, respectively ($P < .05$). Western blot and slot blot analysis showed a corresponding decrease in CYP2C11 protein expression and CYP2C11 mRNA respectively. By ten days of infusion, CYP2C11-mediated PCP metabolism and CYP2C11 expression had returned to normal but CYP2C11-mediated 2α-OH formation was not back to normal until 20 days of continuous PCP infusion. CYP2C11 mRNA levels were decreased throughout the chronic PCP dosing. These data show short term PCP infusions profoundly decrease CYP2C11 function and expression by a pretranslational mechanism, but continued exposure to PCP leads to metabolic tolerance without the recovery of mRNA levels.

BEHAVIORAL EFFECTS AND NMDA ANTAGONIST ACTIONS OF LOW AFFINITY NMDA ANTAGONISTS

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We recently reported that several high affinity uncompetitive NMDA antagonists, as well as memantine (K_i ~ 540 nM; Kornhuber *et al.* 1992) and ibogaine (K_i ~ 1,000 nM; Popik *et al.* 1994) substitute for the discriminative stimulus effects of dizocilpine (K_i ~ 3 nM; Wong *et al.* 1988) in mice (Geter-Douglass and Witkin 1996). Neither dextromethorphan (K_i ~ 3,500 nM; Newman *et al.* in press), amantadine (K_i ~ 10,500 nM; Kornhuber *et al.* 1991) nor ADCI (K_i ~ 11,300 nM; Monn *et al.* 1990) substituted. In the present experiment, dizocilpine produced dose-related increases in ataxia and locomotor activity at comparable doses in mice. These effects distinguish uncompetitive NMDA antagonists from other drug classes (Ginski and Witkin 1994). Conversely, memantine, ibogaine and amantadine produced increases in ataxia at doses that decreased locomotor activity. In a separate experiment, dizocilpine, as well as memantine, ibogaine and ADCI dose dependently blocked NMDA-induced convulsions in mice, whereas neither dextromethorphan nor amantadine did Memantine was protective at doses that did not produce ataxia or increase locomotor activity. This finding supports others who have suggested that antagonists with micromolar affinity for the NMDA receptor-associated ion channel may have therapeutic efficacy for various neurological disorders, including drug abuse without producing the side-effects associated with high affinity compounds (*e.g.,* Rogawski *et al.* 1991; Seidleck *et al.* 1994; Popik *et al.* 1995, 1996). Tests of ataxia and locomotor activity may be sensitive measures to distinguish low versus high affinity uncompetitive NMDA antagonists.

REFERENCES: Available upon request.

IS COCAINE-INDUCED SENSITIZATION A REVERSIBLE PHENOMENON?

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Previous studies have indicated that the co-administration of the noncompetitive NMDA receptor antagonist dizocilpine (MK-801) with cocaine prevents the induction of behavioral sensitization to cocaine and cocaine-kindling. However, from a therapeutic viewpoint it is important to identify agents that could reverse the phenomenon of sensitization once it has been established. In the present study we investigated whether blockade of the NMDA receptor by MK-801 or brain nitric oxide syntbase (NOS) by 7-nitroindazole (7-NI) -- in cocaine experienced animals -- could reverse the sensitization to the convulsive effect of cocaine. Cocaine-kindling was rendered by the administration of 35mg/kg cocaine for ten days to Swiss Webster mice. On day 11 animals were divided into five groups and received the following treatment for the next five days: (1) saline/saline (2) MK-801 (0.3 mg/kg)/saline (3) 7-NI (25 mg/kg)/saline (4) MK-801/cocaine and (5) 7-NI/cocaine. Animals then remained drug free for three days and on day 19, received a challenge injection of cocaine. Results indicated that MK-801 neither prevented the expression of kindled-seizures nor reversed cocaine kindling. However, 7-NI blocked the expression of kindled seizures and also reversed the phenomenon of sensitization to the convulsive effect of cocaine. These results suggest that blockade of the neuronal NOS, but not the NMDA receptor, may set back cocaine sensitization.

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NEUROENDOCRINE AND BEHAVIORAL ACTIONS OF IBOGAINE AND ITS METABOLITE, 12-HYDROXYIBOGAMINE, IN RATS

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Ibogaine (IBO) is an indole alkaloid with putative anti-addictive properties. Recent evidence indicates that IRO is metabolized to 12-hydroxyibogamine (NORIBO) after ip injection in rats. Thus, the spectrum of IBO actions may involve effects of the metabolite. In the present study, we compared *in vivo* actions of IBO and NORIBO in rats fitted with indwelling jugular catheters. IBO (1-10 mg/jg), NORIBO (1-10 mg/kg) or vehicle was administered iv and repeated blood samples were withdrawn. Plasma samples were assayed for corticosterone and prolactin by RIA. Behaviors including locomotor activity, tremors, ataxia, forepaw treading and penile erections were scored in the same subjects. IBO was much more potent than NORIBO as a stimulator of corticosterone secretion, whereas both drugs elevated prolactin to a similar extent. IBO elicited tremors and ataxia at the 10 mg/kg dose, but the metabolite did not. Our data indicate that NORIBO is biologically active. Moreover, the metabolite does not appear to be involved in adverse effects of IBO, *i.e.,* corticosterone release, tremors, ataxia.) Determining the role of nORIBO in mediating the anti-addictive properties of IBO merits further inquiry.

SEX DIFFERENCES IN IBOGAINE ANTAGONISM OF MORPHINE AND IBOGAINE BRAIN LEVELS

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Ibogaine (IBO) is an indole alkaloid currently being investigated for its ability to interrupt opioid and stimulant drug abuse. Previous studies have demonstrated that IBO can decrease morphine (MOR) self-administration, and antagonize MOR-induced dopamine release and MOR-induced locomotor activity. Recently, it has become evident in our laboratory that IBO antagonism of MOR-induced (5 mg/kg ip) locomotor activity varies between the sexes. While IBO (20-60 mg/kg ip) antagonism (5 or 19 hrs) of MOR-induced locomotor activity is evident in female rats (250-275 g), the same doses of IBO appear ineffective in males (275-300 g), who may require higher doses. Consistent with these findings, whole brain IBO levels (1, 5 and 19 hours following 40 mg/kg ip injection) have been determined via gas chromatography-mass spectrometry (GC-MS) and are almost twice as high in female as in male rats receiving the same dose. Preliminary GC-MS studies also indicate that brain levels of a major metabolite of IBO, noribogaine, are significantly higher in females than in males following exposure to IBO (40 mg/kg ip). This difference in both IBO activity and in IBO brain levels between the sexes may help explain some of the inconsistencies in the literature regarding the efficacy of IBO as a potential antiaddictive agent.

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MECHANISM OF ACTION OF IBOGAINE: INTERACTION BETWEEN KAPPA AGONIST AND NMDA ANTAGONIST EFFECTS

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Ibogaine, an alkaloid extracted from Tabemanthe iboga, is being studied as a potential long-acting treatment for both opioid and stimulant abuse. While there have been only anecdotal reports of long-term efficacy in humans, studies in this and other laboratories have shown that ibogaine can decrease both morphine and cocaine self-administration for several days in some rats. Acutely, ibogaine also decreases extracellular levels of dopamine in the nucleus accumbens and striatum while ibogaine pretreatment (19 hours beforehand) blocks morphine-induced dopamine release and morphine-induced hyperactivity. Because ibogaine binds to kappa opioid and NMDA receptors (1-2 μM affinities), we are investigating the role of kappa opioid and NMDA effects in mediating ibogaine's behavioral and neurochemical effects. The results of ongoing studies in rats suggest that both kappa agonist and NMDA antagonist actions of ibogaine contribute to its resultant effects. For example, a combination of nor-BNI (kappa antagonist; 10 mg/kg s.c.) and NMDA (20 mg/kg i.p.) reversed ibogaine antagonism of morphine-induced hyperactivity, while neither nor-BNI or NMDA alone had this effect. Similarly, preliminary results indicate that the combination of nor-BNI and NMDA also blocked ibogaine inhibition of morphine self-administration and ibogaine inhibition of dopamine release in the striatum.

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UNIQUE DISCRIMINATIVE STIMULUS PROPERTIES OF THE COMBINATION OF MK-801 PLUS MORPHINE.

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Tolerance to morphine's (MOR) analgesic effects and sensitization to its locomotor-stimulating effects are each reportedly blocked by the NMDA antagonist MK-801. The molecular mechanisms of this blockade are unknown and-especially in the case of MOR sensitization-are difficult to understand since (i) MK-801 itself has locomotor-stimulating effects that can sensitize with repeated testing; (ii) sensitization to the combination of MK-801 plus MOR occurs more rapidly than to MOR alone; and (iii) rats accustomed to testing with the combination of drugs express sensitization when tested with MK-801 alone but not with MOR alone. We now report that the discriminative stimulus properties of the combination of MK-801 and MOR are fundamentally different from those of either drug alone, which may in part explain why behaviors established in the presence of MK-801 are not expressed in its absence. Rats (n=8) were trained to discriminate the combination of MK-801 (0.05 mg/kg) plus MOR (3.2 mg/kg; drugs administered in a single SC injection) from vehicle in a two-lever food-reinforced discrimination procedure. Treatment with MOR (3.2 mg/kg) alone resulted in vehicle-appropriate responding; MK-801 (0.05 mg/kg) alone partially substituted for the combination of drugs, but this effect diminished with repeated testing. Higher doses of MOR alone also failed to substitute for the combination of drugs. These data suggest that-at the relative doses tested—the discriminative stimulus properties of MOR are obscured by those of MK-801, and raise the possibility that other behavioral changes (*e.g.,* locomotor sensitization) established in the presence of the MK-801 discriminative stimulus are expressed only in its presence.

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THE EFFECTS OF IBOGAINE ON TREMOR AND BALANCE IN COCAINE DEPENDENT PATIENT VOLUNTEERS

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lbogaine has been used abroad in uncontrolled studies as a pharmacotherapy for opioid and cocaine dependence. Concern over potential cerebellar toxicity prompted the present studies of ibogaine's effects on postural stability, body tremor and appendicular tremor. Two doses of ibogaine (1 and 2 mgkg- 1) were administered to nine volunteers with histories of recent cocaine abuse. Static posturography with a portable bedside computerized platform was used to quantity body sway while standing normally and in a heel-to-toe position with eyes opened and eyes closed, Measurements were taken at baseline and every two hours following oral administration of ibogaine. Dynamic posturography measured functional limits of stability over six hrs. Accelerometry was used to measure tremor of the hands at rest and with arms extended over the same time period. Whole body tremor, akinesia, and retropulsion were measure with the Neurotest'FM apparatus at baseline and *48 hours* after drug administration. Both doses of ibogaine produced no clinically visible effects, but static posturography revealed a trend (albeit not significant) toward increased body sway when subjects stood in heel-to-toe posture with eyes closed. Dynamic posturography and the Neurotest measurements revealed no changes from baseline. Hand accelerometry did not show any effects of ibogaine on tremor (at rest or with arms extended). However, baseline measurements of tremor revealed quantitative differences between cocaine dependent patients and age-matched and drug-free control subjects, Power spectrum analysis of these data revealed an increase in the 3-7 Hz range supporting the hypothesis that early cocaine abstinence my reflect a hypodopaminergic state.

SUBSTANCE ABUSE AND MENTAL ILLNESS: WHICH DISORDER CAME FIRST?

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The extensive overlap between mental illness and chemical abuse raises the question of the etiologic relationship between the two disorders. In this paper we are looking for clues to etiology by examining the sequence of family disorganization, the onset of the use *of several types of* drugs, and the first admission to a psychiatric hospital in a sample of 820 homeless mentally ill chemical abusing men studied in New York City between 1991 and 1995. Ages of onset for the use of different drugs and alcohol were found to be interrelated: earlier age of onset for alcohol and marijuana predicted an earlier age of onset for heroin, cocaine and crack use, a finding consistent with the "gateway theory." Onset of mental illness, as defined by first psychiatric hospitalization, usually occurred after the onset of abuse for any of the drugs except crack. *Age of onset* of drug use was also correlated with age of first psychiatric hospitalization the younger the age of onset of marijuana, cocaine, and crack use, the younger the age of first psychiatric hospitalization. Our data suggest that these men started using drags at an early age to alleviate pain and ease sadness and hopelessness. As social mechanisms for early intervention were not available, these men became *chronically disabled,* characterized by poor personal and social functioning. Without adequate social intervention, psychiatric hospitalization became society's response to these men when they reached the stage of total decompensation.

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SOURCES OF DIAGNOSTIC UNCERTAINTY AMONG CHRONICALLY PSYCHOTIC COCAINE ABUSERS

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Diagnostic uncertainty among psychotic drug abusers is a major obstacle to treatment and research. This study developed and tested a diagnostic algorithm to record uncertainty and specify alternate diagnoses. 165 patients with chronic psychoses and cocaine abuse were evaluated using the Structured Clinical Interview for DSM-III-R (SCID), urine toxicology, hospital records and collateral interviews. The algorithm was applied allowing key SCID items and diagnostic criteria to be designated as provisionally met (or uncertain). For these items interviewers specified the source of uncertainty and proceeded with SClD items that would be asked in both the "met" and "not met" conditions. This assessment was repeated Subjects were reassessed 18 months later in an attempt to resolve diagnostic uncertainty. In 30 cases (18%), the initial assessment produced a definitive diagnosis, including 21 cases of schizophrenia, six of schizoaffective disorder and three of psychostimulant induced psychotic disorder. In the other 135 cases, a definitive diagnosis could not be reached because of one or more sources of diagnostic uncertainty, including insufficient abstinence (78%), poor memory (24%) and inconsistent reporting (20%). Reassessment at 18 months led to definitive diagnoses in 12 additional cases. Thus, it was frequently difficult to distinguish schizophrenia from chronic substance induced psychoses, despite the use of structured interviews and reassessment. Clinicians facing such diagnostic dilemmas may conclude prematurely that psychotic symptoms are, or are not, substance induced. Instead, clinicians should initiate concurrent treatment of both psychosis and substance abuse in uncertain cases.

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SYMPTOM PROFILE IN STIMULANT-INDUCED PSYCHOSIS

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OBJECTIVE: to describe the symptom profile of a sample of patients with stimulant-induced psychosis. **METHODS:** Nineteen subjects admitted to a county psychiatric emergency service who had a DSM-IV diagnosis of amphetamine (14)- or cocaine (5)-induced psychotic disorder were evaluated using the Structured Clinical Interview for DSM-IV (SCID-IV) and Positive and Negative Syndrome Scale (PANSS). Reported measures of stimulant use were obtained. RESULTS: Mean age of first drug use was 11 and mean span of stimulant use was 14 years. Lifetime abuse of or dependence on nonstimulant drugs was common (79%). All subjects had positive PANSS Composite scores (Positive minus Negative Scale score). However, some subjects had substantial negative scores, one as high as 27, comparable to the 80th percentile in schizophrenic patients. Also, the majority of subjects had bizarre delusions (95%) and Schneiderian hallucinations (63%). Frequency measures of stimulant use were significantly positively correlated with PANSS Negative Scale score. PANSS Composite score was significantly associated with state of use (intoxication or withdrawal). CONCLUSIONS: The findings support previous reports of the predominance of positive symptoms in stimulant-induced psychosis but also support reports that this disorder can mimic a broader range of schizophrenic symptoms, including substantial negative and bizarre symptoms. Prominant history of other drug use and early age of first drug use may have contributed to the vulnerability of these individuals to psychosis and influenced their presentation. These findings suggest that state of intoxication or withdrawal and substance use history may influence symptom presentation and be important in differential diagnostic considerations.

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SIMILAR RESPONSES TO COCAINE CHALLENGE IN ANTISOCIAL AND NON-ANTISOCIAL COCAINE ABUSERS

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Antisocial personality disorder (APD) is much more prevalent among cocaine abusers than among the general population and appears to be a prominent risk factor for development of cocaine abuse. This study addressed whether this epidemiological relationship is associated with differences in response to cocaine administration. Acute cocaine dose-effect data were selected for 33 cocaine abusers who had participated in any of six prior studies. APD diagnostic assessment (by SCID structured interview) had been performed prior to participation (N=13 with APD diagnosis; N=20 non-APD). For each volunteer data were examined for three intravenous cocaine challenge conditions -- zero, low and high dose (saline placebo, 20-25 mg cocaine, and 40-50 mg cocaine, respectively). The profile and time course of an array of physiological and subjective indices of cocaine effects were compared for APDs versus non-APDs. In both groups there were significant dose-dependent changes in cardiovascular measures, pupil diameter, and subjective responses characteristic of cocaine effects. There were no significant differences in physiological or subjective responses to cocaine as a function of APD diagnosis, though there was a nonsignificant trend for ASP subjects to have a more pronounced subjective response to the low cocaine dose. If cocaine abusers with versus without APD do not differ in their responses to cocaine this suggests that the epidemiological association of APD and cocaine abuse may result from nonpharmacological factors.

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PSYCHOSIS, MOOD AND QEEG IN CRACK COCAINE ABUSERS

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Psychosis is a well known complication of chronic stimulant abuse. In the context of our ongoing study of crack cocaine users in residential treatment, we compared quantitative EEG (qEEG) measures in 22 subjects disclosing a history of visual or auditory hallucinations while on crack cocaine (hallucinations +) versus 40 subjects denying such a history (hallucinations -). Consistent with work previously published by ourselves and others, both groups of crack cocaine users showed reduced absolute power in delta and theta, however the slow wave deficit was significantly attenuated in the hallucinations + group relative to the hallucinations - group. Mean scores in Beck Depression Inventory were 18.6 in the hallucinations + versus 11.4 in the hallucinations - group (p=0.013). The two groups did not differ with respect to age, gender, years of education or measures of intensity of use or cumulative exposure to cocaine or other drugs of abuse. These results can be interpreted according to a model in which sensitization of the mesotelencephalic dopaminergic projections is further potentiated by depression. One salient implication of this interpretation is that as a psychopathological model, cocaine induced psychosis may relate more closely to mood disorder with psychotic features than to schizophrenia.

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AUTONOMY OF PSYCHIATRIC SYMPTOMS AMONG COCAINE USERS

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This study addresses the degree to which psychiatric disorders are autonomous from drug or alcohol use. Autonomy ratings for 91 cocaine-using methadone patients with a SCID derived mood (77%) or anxiety (56%) disorder were obtained. Subjects were rated as either having low (41%) and high (59%) autonomy. Subjects were 56% male, 85% African-American or Hispanic, mean age 37 and were about to start a 6-month treatment program for cocaine dependence. Days used drugs/alcohol in the past 30 days were: 18 days for cocaine, four for heroin, four for marijuana and five for alcohol. Treatment completion rate was 65%. Autonomy ratings for mood and anxiety disorders were not associated with age, sex, ethnicity, mood (Profile of Mood States) or symptom severity (Brief Symptom Inventory). However, greater autonomy was inversely associated with days used cocaine, marijuana, and alcohol. There was a positive association between autonomy and completing treatment. (Hispanic ethnicity and mood disorder were the only other variables associated with completing treatment.) The impact of autonomy on treatment completion was further examined in a logistic regression analysis with treatment completion as the dependent variable and autonomy, mood diagnosis, anxiety diagnosis, and Hispanic ethnicity as the independent variables; autonomy emerged as the only significant predictor of retention. These results suggest that comorbid substance abusers who report psychiatric symptoms during periods of non-drug use are likely to be using less drugs and are more likely to complete drug treatment than comorbid patients whose symptoms are not autonomous.

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PSYCHOLOGICAL AND EVENT HISTORY OF FEMALE METHADONE CLIENTS

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Comorbid psychopathology is relatively common in male and female substance abusers. In addition, combat-related post-traumatic stress disorder (PTSD) and substance abuse/dependence have been specifically linked in men. Very few authors have examined these diagnoses in women. The present study investigates the prevalence of psychological diagnoses, including PTSD, in women in methadone maintenance treatment (MMT). To date, 40 women have been interviewed with the Structured Clinical Interview for DSM-IV, Patient Edition. 60% of the sample have current or lifetime major depressive disorder (MDD) and 20% have a history of social phobia. 10% have lifetime panic disorder and 5% have a history of significant organic psychotic symptoms. Only 5% meet. criteria for Antisocial Personality Disorder (ASPD). Of those 40, 31 women have also received a structured interview assessing lifetime history of PTSD events and diagnosis. Clients reported experiencing an average of 13 traumatic events each 74% of the sample have a current or lifetime diagnosis of PTSD. Fully 64% of women exposed to sexual assault (SA) developed PTSD in response. Of those women with a history of SA, each had experienced an average of 3.6 assaults. The second highest PTSD rate was seen in physical assault (PA), with 25% of those exposed developing PTSD. Women with a history of PA had experienced an average of 3.1 assaults. Clients with PTSD were no more or less likely to have other psychological disorders. Interestingly, clients were somewhat more likely to have had PTSD before they began abusing opiates, but were more likely to have begun abusing opiates before they developed MDD. These results suggest 1) the prevalence of psychological diagnoses in this sample is similar to that seen in other studies, 2) women in MMT have experienced an alarming number of PTSD events and have extremely high rates of PTSD, especially to sexual assault, and 3) PTSD may be more strongly linked to the onset of substance abuse/dependence in this population than other psychological disorders. It is suggested that this data should influence future assessment and treatment of female methadone maintenance clients.

WHAT IS "TREATMENT AS USUAL" FOR BIPOLAR SUBSTANCE ABUSERS?

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As part of a study to develop a relapse prevention group therapy for bipolar substance abusers, we examined a control group of such patients receiving "treatment as usual" (TAU). To define further what TAU is for this population, we followed 24 recently hospitalized patients monthly for six months, using the Treatment Services Review. We hypothesized that these patients would have little integrated treatment for the two disorders. We found that all patients but one received medication for bipolar disorder throughout the course of the six months; individual psychotherapy was the most common behavioral treatment (46% of patients). Only one patient ever attended group therapy and three had couple or family therapy. Sixty-seven percent attended AA during the first post-hospital month; this figure dropped steadily to 42% at six months. NAKA attendance similarly dropped over time from 38% in the first month to 17% at six months. Indeed, all behavioral treatment attendance was at its lowest at six months. This study shows a pattern of relatively infrequent behavioral treatment (except for individual therapy) in this population, with a diminishing use of behavioral treatment over time.

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PSYCHIATRIC CO-MORBIDITY OF DUALLY DEPENDENT (OPIATE AND COCAINE) OUTPATIENTS: CORRELATIONS WITH TREATMENT COMPLIANCE

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Lifetime prevalence of psychiatric co-morbidity is high among substance abusers and seems to affect treatment outcome. The purpose of this study was to investigate the lifetime prevalence of psychiatric disorders among individuals diagnosed with dual dependence (cocaine plus heroin) and the relationship with outpatient buprenorphtne treatment compliance. The parent study evaluated the safety and efficacy of four different dose schedules of a 70-day program with buprenorphine plus counseling for treatment of outpatients who met DSM-IIIR criteria for both opiate and cocaine dependence. All subjects were administered the Diagnostic Interview Schedule (DIS) prior to admission. One hundred and ninety-seven dually dependent outpatients (mean [±SD] age 34.0 ± 6.4 years, 75% African-Americans, and 66% males) were interviewed, It was found that 167 (84.8%) had at least one other psychiatric disorder. The commonest disorders were tobacco dependence (660%), alcohol dependence (45.7%) cannabis dependence (29.4%), phobic disorder (21.8%), and antisocial personality disorder (ASP) (20.3%). The prevalence of comorbid mental disorders among those with alcohol disorder was 10.2% and with a drug problem (except tobacco) was 5.1%. Comparisons with results of the ECA study will be presented. Bivariate analysis showed that individuals with ASP had a significantly ($p<0.05$) lower proportion of completers and lower survival in treatment. These findings suggest that dually dependent outpatients have a high prevalence of other psychiatric disorders, higher than has been reported for the general population, and that ASP is a predictor of poor treatment compliance.

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ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IS ASSOCIATED WITH EARLIER ONSET SUBSTANCE ABUSE

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We evaluated the association between ADHD and the age of onset of the psychoactive substance use disorders (PSUD) in adults with ADHD attending to issues of psychiatric comorbidity. We hypothesized that ADHD and psychiatric comorbidity would be risk factors for early onset PSUD. We compared findings in 120 referred adults with a clinical diagnosis of childhood-onset ADHD with those of a sample of non-ADHD adult comparisons (N=268). All diagnoses were obtained using DSM III-R based structured psychiatric interviews. To index onset of PSUD, we used comparisons of age of onset, rates of adolescent onset, and Cox proportional hazard models. ADHD was associated with an earlier onset of PSUD than non-ADHD controls independently of psychiatric comorbidity ([mean±SD] 19.1±7.1 vs 22.0±8.2 years, $p<0.05$). Conduct and juvenile bipolar disorders conferred a significantly increased risk for very early onset PSUD independently of ADHD. Psychiatric disorders commonly emerged prior to the onset of PSUD in all subjects. ADHD persistent into adulthood with and without psychiatric comorbidity was associated with adolescent onset PSUD. In addition, comorbidity with conduct and juvenile bipolar disorder were risk factors for very early onset PSUD in both ADHD and non-ADHD individuals. These findings confirm and extend previous findings documenting important associations between ADHD and PSUD.

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ADHD IN OPIOID ABUSERS ENTERING OPIOID SUBSTITUTION TREATMENT

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Objective- New admissions to a community based opioid substitution treatment clinic were evaluated for attention-deficit/hyperactivity disorder (ADHD). *Methods*- After a one month stabilization period, patients were evaluated for ADHD using the ADHD module of the Diagnostic Interview Schedule. Parents of patients with definite or possible ADHD were contacted to confirm the diagnosis. All patients also completed the Continuous Performance Task (CPT), a sensitive and objective measure of attention. They also received an extensive assessment battery including the ASI and the SCID I and II. *Results*- Eighteen percent (13/72) met childhood criteria for ADHD, and 4% (3/72) met criteria for a current diagnosis. The ADHD group showed higher lifetime rates of major depression (39% vs. 15%, p=.05), antisocial disorder (46% vs. 25%, p=NS), anxiety disorder (31% vs. 9%, p=NS), and cannabis dependence (54% vs. 26%, p=.05). There were no significant differences between groups on any ASI domain. Fifty-four percent (7/13) of those diagnosed with childhood ADHD were female, a much larger percentage than seen in psychiatric clinics or reported in other studies of substance abusers. Of three CPT tasks (AX, audio, and degraded X), only the AX task showed significant differences between groups. Conclusion- A substantial minority of patients entering opioid substitution treatment had a childhood history of ADHD, most are female, serious psychiatric comorbidity is common, and certain attention deficits persist into adulthood.

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MMPI PROFILES OF METHADONE- MAINTENANCE PATIENTS: PREDICTING RESPONSE TO TREATMENT

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Though previous studies have used MWI data to classify opiate users into subgroups, the predictive validity of such groups is seldom assessed. In this study, we used cluster analysis to identify four MMPI profile types that predicted differential response to methadone maintenance treatment. Subjects completed MMPIs one month after treatment entry. K-corrected T scores from 13 MMPI scales were cluster analyzed using Wards method. Two groups produced mean MMPI profiles with no significant ($T \geq 70$) clinical scale elevations. Of these two "normal" groups, Cluster I (*n* - 25) was distinguished from Cluster 3 (n = 37) by a more defensive validity scale configuration and by lower *Ma* and MacAndrew Alcoholism (MAC) scale scores. Of the remaining groups, Cluster 2 (*n* = 36) obtained the highest mean profile with significant elevations on six of ten clinical scales. Cluster 4 (*n* - 53) obtained moderate scores on most scales, though only *Pd and MAC* scale scores were significantly elevated. Demographic data and intake ASI composite scores served to externally validate cluster groups. Clusters did not differ with respect to age, race, or sex but differed in five of seven ASI problem areas: Legal, Family/Social, Psychological, Employment, and Alcohol. Treatment response was assessed by aggregating urinalysis results over 64-week intervals. Though groups did not differ during the pre-test period, Cluster I subjects submitted significantly more drug free urines than other subjects during four of five post-test intervals. Other than Cluster 1, only Cluster 2 improved significantly over time, even though these subjects were the most psychologically disturbed. Cluster 3 failed to improve despite relatively low severity of psychological and psychosocial problems. The results suggest that personality functioning can predict treatment outcome and that the relationship between psychological problems and outcome is more complex than is commonly assumed.

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LONG-TERM TEST-RETEST RELIABILITY OF PERSONALITY DISORDERS IN METHADONE MAINTAINED PATIENTS

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This study examined the two year test-retest reliability of DSM-III-R personality disorder (PD) diagnoses in a sample of 172 opiate dependent men admitted to methadone treatment. Different M.A./Ph.D. interviewers at each assessment used a semistructured diagnostic interview for PDs, the Structured Interview for DSM-III-R Personality (SIDP-R), to make their diagnoses. The reliability of any PD diagnosis was fair (k = .50). When finer cuts were made reliabilities were not as high. Three individual Cluster B PDs, antisocial (k = .43), borderline (k = .42) and narcissistic (k = .42), were the only specific PDs for which at least fair reliability was achieved. At the cluster level, only Cluster B had acceptable reliability (k = .47). Number of symptoms of the individual PDs was significantly and moderately correlated at the two assessment points. Insofar as the base rates of most PDs were low and agreement for no PD diagnosis tended to be very high, percent agreement typically exceeded 90% for the individual PDs. Increasing the base rate by lowering the diagnostic threshold or looking at agreement with more severe cases by raising the diagnostic threshold did not substantially or predictably effect reliabilities for the individual PDs. The reliability coefficients, although modest, are in the range of longer interval test-retest reliabilities for PDs found in general psychiatric patient samples.

THE CONCURRENT VALIDITY OF SUBSTANCE USE DIAGNOSES IN OPIOID DEPENDENT OUTPATIENTS

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The present study evaluated the relationship between SCID-based substance use diagnoses and drug use early in treatment among opioid abusers in methadone substitution therapy. New admissions (N = 138) were assessed via the Structured Clinical Interview for the DSM III-R (SCID) for presence of Axis I and Axis II disorders and followed for five weeks on standard methadone maintenance. Patients submitted urines three times per week tested for opioids, cocaine, and benzodiazepines. Patients diagnosed with current cocaine use disorder (n = 90) submitted a higher proportion of cocaine-positive urines (M = .84) than patients diagnosed with past cocaine use disorder (n = 34; M = .28) and those diagnosed with no cocaine use disorder (n = 14; M = .12), p < .001. Current cocaine use diagnosis accounted for 51% of the cocaine use variance. Patients exhibiting a current sedative use disorder (n = 25) submitted a higher proportion of benzodiazepine-positive urines (M = .60) than patients with a past sedative use disorder (n = 53; M = .20) and those with no sedative use disorder (n = 60; M = .05), p < .001. Current sedative use diagnosis accounted for 34% of the benzodiazepine use variance. Lifetime major depression (12%) and antisocial personality disorder (39%) were the most common nonsubstance use comorbid diagnoses. Diagnosis of an Axis I or Axis II nonsubstance use disorder was associated with benzodiazepine, but not cocaine use early in treatment (p < .05). These data demonstrate the concurrent validity of SCID-based cocaine and benzodiazepine use diagnoses, and point toward a potentially important relationship between benzodiazepine use and other psychiatric disorders.

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RELATIONSHIP OF COMORBIDITY TO HIGH RISK DRUG USE, SEXUAL PRACTICES, AND VIOLENCE AND VICTIMIZATION AMONG SEVERELY MENTALLY ILL ADULTS

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Risk for HIV infection and the incidence of violence and victimization have been understudied among individuals with serious mental illness. The purpose of this study was to examine the relationship between high risk drug use, high risk sexual practices, and violence and victimization in a sample of frequently hospitalized psychiatric clients of an urban case management program. It was hypothesized that subjects with co-occurring substance dependence disorders would be at greater risk for HIV and have a higher incidence of violence and victimization than non-dependent subjects. Substance dependence was determined through the administration of the QDIS3R, a “quick” version of the DIS-III-R. Subjects completed the Risk Assessment Battery (RAB) and the MacArthur Community Violence Instrument. To date, 38 subjects have completed the study. Results indicate that substance dependent subjects were significantly more likely to engage in high risk drug and sexual practices than nondependent subjects. Dependent subjects were also five times more likely to commit a violent act in the past 12 months.

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DEPRESSED MOOD AND SELF-MEDICATION IN LONG-TERM USERS OF CODEINE

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The per capital use of codeine exceeds the expected use based upon the frequency of disorders for which codeine has approved indications. This suggests that use is for other symptoms. To characterize this use, 339 long-term users of codeine (alone or in combination) willing to complete an anonymous questionnaire were recruited by advertisements. Of this group, 64% had sought help for mental health problems; 56% had visited a psychiatrist/psychologist; 15% had been hospitalized for psychiatric problems; 14% were currently taking antidepressants; and 32% had at least one family member with a psychiatric problem (46% depression). Reasons for use varied, but 18% reported using codeine for relaxation; 11% for insomnia. DSM-IV criteria for dependence were met by 126 (37%). Codeine use represented a "problem" for 60% of dependent (D) subjects, but only 7% of non-dependent (ND) subjects ($p < 0.001$). Compared to ND, the D users: were younger; used more codeine per day (median 120 vs. 60 mg/day); had more psychological consequences of use; used more illicit sources; and used more mental health services (all $p < 0.05$). D and ND subjects were similar in age of first use (26) sex (female 51%) years of regular use (11.5), reasons for initial use, and general health status. Among the D users, lifetime depression (53% vs. 37%) and other substance use disorders (27% vs. 6%) were significantly more common. D subjects attributed a greater number of psychological problems to the codeine than the ND subjects (e.g. depression 23% vs. 4%). On the SCL-90, D subjects had higher mean scores on the Global Severity Index (1.16 ± 0.67 vs. 0.69 ± 0.69) and depression subscale (1.53 ± 0.97 vs. 0.88 ± 0.84). These data show that a substantial number of chronic codeine users are dependent, have depression and may use codeine for mood modulation. The high frequency of depressive symptoms and disorders suggests antidepressants should be considered as a treatment option. Supported in part by NIDA grant DA06889.

PRESCRIBING PATTERNS OF POTENTIAL DRUGS OF ABUSE IN A GENERAL PSYCHIATRIC HOSPITAL

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A number of studies have addressed physician variables which affect prescribing patterns, and a wide variation of all classes of drugs between practitioners and practices has been recognized. Research looking at patient variables and their influence on physician prescribing patterns appears to be minimal, however. This study examined the patient variables (age, gender, ethnicity, and diagnosis) surrounding the prescribing of controlled substances in a general psychiatric hospital. Controlled medications were chosen since these drugs have the potential to be inappropriately prescribed, over-prescribed, misused, or abused. The total number of discharge prescriptions (n=1,247) over a 6-month period was analyzed. The distribution of prescriptions written for controlled vs. non-controlled medications by the four patient variables was determined. Overall, the prescribing of controlled substances in the hospital was low. Most prescriptions were for the *18-50* age group, but the proportion of controlled vs. non-controlled prescriptions was similar in each age group. No differences were found between genders. There were some prescribing differences by ethnicity with a smaller proportion of black patients receiving controlled vs. non-controlled medications when compared with white, Hispanic and other patients groups (Chi Square=8.842, df=3, p=.0314). It is also noted that a significantly high proportion of controlled medications were prescribed for patients (0-18 age group) diagnosed with a Disorder of Infancy, Childhood, and Adolescence when compared with other diagnostic groups (Chi Square=23.047, df=4, p=.00012). The most prescribed controlled drug for this patient group was methylphenidate, commonly used to treat those diagnosed with Attention-Deficit and like disorders. Further investigation with a larger, and more diversified patient population is recommended. A survey of physicians' attitudes and beliefs regarding the writing of prescriptions for controlled vs. non-controlled medications for different age, gender, and ethnic groups may also be revealing.

FENFLURAMINE EFFECTS ON IMPULSIVITY OF ADULTS WITH HISTORY OF CONDUCT DISORDER AND MATCHED CONTROLS

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Ten males with a history of childhood conduct disorder and ten matched controls will participate after giving their informed consent. Subjects were excluded if screening indicated any history of medical or axis-1 psychiatric disorders or recent drug usage detected by urine drug screen analysis. Subjects participated two or three days per week for four weeks. During each day, six sessions were conducted between 8am-3pm in which impulsivity was assessed using a self-control paradigm. Each session consisted of 50 trials in which they were given choices between a small reinforcer of five cents available after a short delay of five seconds (impulsive option) or a larger reinforcer of 15 cents available after a longer variable delay (self-control) option. The delay for the smaller reinforcer remained fixed at live seconds, while the delay for the larger reinforcer began at 15 seconds, and was increased by two seconds each time the subject selected the larger reinforcer and was reduced by two seconds each time the subject selected the smaller reinforcer. After two baseline days, subjects received 1-2 placebos and one fenfluramine dose per week. The fenfluramine doses were 0.212, 0.425 and 0.85 mg/kg given 30 minutes before the first session of the day. Fenfluramine produced dose-related decreases in the number of impulsive (5 cents after five seconds) choices and increases in the length of the longest delay tolerated for the 15 cent reward. These effects indicate a reduction in impulsiveness as assessed by this behavioral procedure. This effect was more consistent and larger in subjects with a history of childhood conduct disorder.

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BEHAVIORAL AND BIOLOGICAL DIFFERENCES BETWEEN DRUG DEPENDENT AND NON DRUG USING FEMALES

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To further the understanding of drug dependence in females, 17 females with either a history of drug dependence or no past drug use were recruited into a larger study of drug dependence. The first two days of testing, aggression (© Point Subtraction Aggression Paradigm) and impulsivity were measured using computer paradigms. In the aggression paradigm subjects could aggress toward another person by taking away money. In the impulsivity paradigm, subjects chose between a larger more delayed reinforcer (15¢, after 15 sec.) and a smaller, more immediate reinforcer (5¢ after 5 sec.). When the subject chose the delayed reinforcer, the subsequent delay for that reinforcer was increased by two seconds. In the last two days, the serotonergic system function was assessed by measuring the hypothalamic-pituitary hormone release (cortisol) following acute stimulation of the serotonin 5HT1a receptor subsystem by ipsapirone. The magnitude of cortisol secretion was taken to indicate the sensitivity of the postsynaptic receptor system. Results showed that females with a history of drug (but no current use) are more aggressive than females with no history of any illicit drug use, but that impulsivity and 5HT1a receptor function did not differ between these groups. Aggression has been previously noted as a precursor to drug use in males, and this may suggest that it is so for females also. Previous reports that have related serotonergic function to drug dependeme were not replicated here, although it is notable that the serotonergic system does not seem to have recieved long term damage as a result of chronic drug use.

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EFFECTS OF ANABOLIC STEROIDS ON AGGRESSIVE RESPONDING IN HUMANS: IS THERE A DOSE-RESPONSE?

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We have previously shown in our laboratory that administration of supraphysiologic doses (600 mg/wk) of testosterone cypionate significantly increases aggressive responding in male volunteers (Kouri et al., 1995). The present study was conducted to determine if lower doses of testosterone (300 mg/wk), also altered aggressive responding. Male subjects between the ages of 23-36 received gradually increasing doses of testosterone (150 mg/wk for two weeks, 300 mg/wk for two weeks and 600 mg/wk for two weeks) or placebo using a double-blind, randomized, cross-over design. Subjects were tested prior to testosterone administration and then one week after the last injection of 300 mg and 600 mg. During each session, subjects could press a button to accumulate points exchangeable for money or press another button to subtract points from a fictitious person (aggressive response; Cherek et al., 1989). Aggressive responding was instigated when the fictitious opponent subtracted points from the subject. Our results indicate that aggressive responding after the 300 mg dose is not different from baseline or placebo responding. However, the 600 mg dose significantly increases aggressive responding. In addition, subjects were given an expectancy questionnaire. There was no significant correlation between subject's expectancies and aggressive responding in the computer test. In conclusion, the effects of anabolic steroids on aggression appear to be primarily related to the dose administered and cannot be explained by the subjects' expectancies.

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ANGER MANAGEMENT TREATMENT IN CULTURALLY DIVERSE SUBSTANCE ABUSE PATIENTS

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Developing substance abuse treatments that are culturally competent is an important issue. Treatments must be effective for individuals of different cultures, ethnic backgrounds, and social classes. However, culturally specific treatments may not be necesssary in all clinical situations. In this presentation we examined the generalizability of a 12-week cognitive-behavorial anger management group treatment for substance abuse patients. A sample of 44 Caucasian patients was compared to 21 African-American patients on the extent to which they reduced their anger. All participants were male veterans enrolled in substance abuse treatment at the San Francisco Department of Veterans Affairs Medical Center. Measures of self-reported anger were taken on the first, sixth, and twelfth weeks of treatment. Self-reported anger was measured with the State-Trait Anger Expression Inventory and the anger-subscale of the Profile of Mood States. Although African-American patients showed significantly ($p < .05$) lower levels of trait-anger during the first week of treatment, African-American patients did not differ from Caucasian patients on the extent to which they reduced anger. All participants reduced their anger significantly (p .05) after the end of the 12-week treatment. These findings show that the 12-week anger management treatment is effective for English speaking African-American patients, as well as Caucasian patients. These findings also suggest that no special culturally specific anger management protocol is required to assist the average African-American male patient.

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ANGER MANAGEMENT STRATEGIES ASSOCIATED WITH DECREASED ANGER IN SUBSTANCE ABUSE PATIENTS

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In their relapse-prevention model, Marlatt and Gordon reported that the most prevalent high-risk situation for relapse was dealing with frustration/anger. They suggested that treatment should focus on teaching patients coping skills to manage these high-risk situations. In a non-clinical sample of middle-class adults, Lazarus and Folkman (1985) demonstrated that anger was positively correlated with distancing and confrontive coping and negatively correlated with planful-problem solving and positive reappraisal. We extended Lazarus and Folkman's model of coping and emotion to a sample of 20 substance abuse patients who completed a 12-week cognitive-behavioral anger management treatment at the San Francisco VA Medical Center or the San Francisco General Hospital. The Ways of Coping Questionnaire was adapted to reflect cognitive-behavioral strategies of managing anger. Interviewers asked patients to report the frequency they used each anger-management strategy during the past month at the beginning and end of the 12-week treatment. Consistent with findings of Lazarus and Folkman, decreases in anger across the 12-week treatment were associated with increased use of positive reappraisal and planful problem solving. Increases in anger were associated with confrontive coping. Behavioral strategies associated with decreases in anger were the use assertive behavior and trying to process anger-provoking situations instead of acting impulsively. The anger management treatment directly produced decreases in the use of displacement for managing anger and produced an increase in the extent patients processed anger-provoking situations.

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SUBSTANCE USE ASSOCIATED WITH DECREASED ANGER ACROSS A 12-WEEK COGNITIVE-BEHAVIORAL ANGER-MANAGEMENT TREATMENT

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In previous presentations, we demonstrated that a 12-week cognitive-behavioral anger management treatment produced decreased levels of anger in substance abuse patients. We did not address the impact of decreased levels of anger on substance use, however. In this study, we present preliminary data from a sample of 55 substance abuse patients who enrolled in a 12-week anger management treatment; 65% of the sample (35 patients) completed treatment. All patients had a diagnosis of cocaine abuse and were enrolled in substance abuse treatment. Levels of anger were measured monthly with self-report questionnaires and drug use was measured weekly with self-report and urine toxicology screening. Consistent with our previous studies, the 35 patients who completed treatment showed a significant ($p<.05$) decrease in trait-anger and anger-expression. Interviews administered at the beginning and end of treatment showed significant decreases ($p<.05$) in the frequency of displaying aggressive behaviors, frequency of thinking irrational beliefs, and frequency of reacting to anger-provoking situations. These decreased levels of anger were associated with abstinence. Of the 35 substance abuse patients who completed the 12 week treatment, 32 abstained from all illicit drugs, and only one patient used cocaine. These findings suggest that our anger management treatment produces both decreased levels of anger and decreased substance use.

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METHAMPHETAMINE-INDUCED DECREASES IN TRYPTOPHAN HYDROXYLASE ACTIVITY AND THE ROLE OF 5-HYDROXYTRYPTAMINE TRANSPORTERS

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It has been suggested that methamphetamine (METH)-induced 5-hydroxytryptamine (5HT) neuronal damage is caused by transport of large quantities of newly released dopamine (DA) from extracellular spaces into 5HT terminals. This hypothesis is based on the findings that: 1) DA is required for METH-induced 5HT neuronal damage; 2) 5HT uptake inhibitors such as fluoxetine attenuate METH-induced decreases in brain tryptophan hydroxylase (TPH) activity; and 3) fluoxetine blocks [^{3}H]DA uptake into synaptosomes prepared from tissue populated with 5HT transporters. The present data confirm and extend these findings by demonstrating that fluoxetine: 1) prevents METH-induced decreases in TPH activity in rat striatum, hippocampus and frontal cortex; and 2) blocks [^{3}H]DA uptake into synaptosomes prepared from these brain regions. The hypothesis is not, however, supported by the findings that: 1) parachloroamphetamine-induced 5HT neuronal damage does not affect [^{3}H]DA uptake into synaptosomes prepared from these brain regions, and 2) citalopram, a compound similar to fluoxetine in 5HT transporter affinity, has an IC_{50} for [^{3}H]DA uptake into striatal, hippocampal and cortical synaptosomes far greater than that of fluoxetine. These data suggest that 5HT transporters may not contribute significantly to [^{3}H]DA uptake in these brain areas. Hence, METH-mediated 5HT neuronal damage may be mediated by effects unrelated to uptake of DA by 5HT transporters.

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THE ROLE OF DOPAMINE IN MEDIATING, THE EFFECTS OF METHCATHINONE

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Methcathinone ("CAT") is a synthetic; derivative of cathinone, an amphetamine-like compound found naturally in the "khat bush," or *Catha edulis*. During the early 1990s, CAT appeared as an illicit drug of abuse in the U.S. and was designated a Schedule I compound in 1993. The mechanism by which CAT elicits its stimulating effects is unknown, however, other stimulants such as methamphetamine induce dopamine (DA) release which appears to mediate their monominergic toxicity as measured by decreases in the activity of their respective synthesizing enzymes. We employed microdialysis to assess the striatal response to three different doses (10, 20, and 30 mg/kg) of CAT and found a dose-dependent increase in DA release. Further, we observed that the selective D-1 antagonist, SCH 23390 (0.5 mg.kg), and the selective D-2 antagonist, eticlopride (0,5 mg/kg), blocked the decrease in tyrosine hydroxylase activity caused by four doses (4-hr intervals) of CAT. In contrast, the decrease in tryptophan hydroxylase activity caused by CAT treatment was attenuated by D-2 blockade, but unaffected by the D-1 antagonist. Our findings demonstrate that CAT increases extracellular striatel DA. Increased DA activity caused by CAT is involved in its neurotoxic effects on the dopaminergic system of the striatum through D-1 and D-2 receptors. However, these receptors do not appear to be is important for the CAT-induced serotonergic toxicity.

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INTERACTION OF *k*-OPIOID AGONISTS AND COCAINE ON DOPAMINE NEUROCHEMISTRY: CHARACTERIZATION BY QUANTITATIVE MICRODIALYSIS

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Kappa-opioid agonists prevent behavioral sensitization and the enhanced dopamine (DA) ovefflow that occurs in response to repeated administration of cocaine (Shippenberg and Heidbreder 1995; Heidbreder, *et al.1995).* This study ‘used the quantitative microdialysis method of Lönnroth *et al.* (1987, 1989) to examine further the action of *k*-opioid agonists on DA neurochemistry. An estimate of extracellular concentration (DA_{ext}) and extraction fraction (E_d) of DA was obtained (Bungay *et al.* 1990). E_d, a measure of *in vivo* recovery, has been shown empirically to be an index of DA uptake activity in the rat (Justice 1993). Therefore, the use of this quantitative microdialysis method provides data on DA extracellular concentration, DA uptake, and, by inference, DA release. Measurements were made under basal conditions in rats 72 hrs after cessation of a 5-day treatment with either U-69593 (0.32mg/kg/day) or vehicle in combination with saline or cocaine (20mg/kg/day). In parallel groups of rats, cocaine treatment alone yielded robust behavioral sensitization that was completely blocked by concurrent U-69593 treatment (U69593/cocaine). No differences among treatment groups in DA_{ext} were observed. In contrast, E_d varied significantly, such that vehicle/cocaine treatment increased Ed (43 ± 12%) and U-69593/saline pretreatment decreased E_d (11 ± 1%) relative to veh/saline controls (24 ± 3%). Importantly, E_d in U-69593/cocaine pretreated rats was not increased (21 ± 4%) and did not differ from controls. Changes in DA release among treatments groups equaled the changes in E_d, as suggested by the unaltered levels of DA_{ext}. These findings confirm previous reports showing an increase in DA turnover in n.accumbens after cessation of a repeated intermittent cocaine treatment (Parsons *et al.* 1991; Kalivas and Duffy 1993). In addition, these data show that concurrent *k*-opioid agonist treatment prevents these changes in dopamine neurochemistry. It is suggested that the action of *k*-opioid agonists on DA uptake and release opposes that of cocaine, and thereby prevents the neurochemical changes that mediate behavioral sensitization to cocaine. References are available upon request from AC Thompson.

ACTIVITY OF NEURONS IN THE NUCLEUS ACCUMBENS CORRELATED WITH COCAINE-SELF INFUSION: RELATIONSHIP TO BEHAVIOR DURING THE INTERINFUSION INTERVAL

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The firing rates of single neurons in the Nucleus Accumbens (NAcc) of rats were recorded extracellularly during intravenous cocaine self-administration (fixed-ratio 1; 0.7 mg/kg/inf). For 65% of responsive neurons, firing rate changed during the 1-2 min postpress. This change was reversed progressively during the interinfusion interval (III), such that firing reattained prereinforcement rates shortly before the next lever press. Analysis of time stamped videotapes showed that the percent of time that rats spent in locomotion, including that related to the lever wall, increased during later portions of the III. Although the total percent of time that rats spent in focused stereotypy decreased as the III elapsed, the proportion of stereotypy that occurred proximal to the lever wall tended to increase. The changes in locomotion may be related to the changes in firing rate. However, neural firing rates during locomotor events did not differ reliably from rates during temporally matched stereotypy events. Moreover, the neural pattern was replicated when firing rates pre- and postpress were calculated using only periods of homogenous behavior (i.e, stereotypy). The present data indicate that the progressive reversal firing pattern does not reflect firing time locked to the execution of locomotion but could reflect processing that contributes to the induction of locomotor and/or goal (cocaine)-oriented behavior. Such a relationship would be consistent with the hypothesis that the progressive reversal contributes to the transduction of declining drug levels into an increased bias to engage in drug-related appetitive behavior.
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MARKED DEPLETION OF DOPAMINE D_2 RECEPTORS AFTER ADMINISTRATION OF A SELECTIVE KAPPA OPIOID AGONIST

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U-69593 (0.32 mg/kg), the selective kappa opioid agonist, was repeatedly administered in single daily injections to male, Sprague-Dawley rats. Two or ten days later, the rats were euthanized and dopamine D_1 and D_2 receptors were measured using [^{3}H]SCH 23390 or [^{3}H]sulpiride, respectively, in caudate putamen and nucleus accumbens. Saturation curves using increasing concentrations of labeled ligand were constructed and analyzed via Scatchard transformations so that K_D and B_{max} values could be determined. Two days after the last of three injections, dopamine D_2 receptors in the caudate putamen were decreased by approximately 40%, with no change in D_1 receptors. In the nucleus accumbens, there was a small, but not statistically significant decrease in dopamine D_2 receptors. There appeared, however, to be a rebound effect such that dopamine D_2 receptor number was greatly increased in the nucleus accumbens after ten days of withdrawal. In contrast, no changes in either receptor subtype were seen when receptors were measured either one day after the three injections, or two days following a single injection of U-69593. Furthermore, there were no differences in either the total amount of dopamine taken up or in the 100 for cocaine to inhibit dopamine uptake following this treatment, suggesting that the dopamine transporter and presynaptic terminals were intact. These effects cannot be attributed to a direct action of U-69593 at dopaminergic sites since this compound did not bind to dopamine D_2 receptors, or inhibit dopamine uptake. These findings suggest a potential mechanism by which kappa opioid agonists attenuate the behavioral effects of cocaine.

TOLERANCE TO THE INHIBITION OF DOPAMINE UPTAKE BY COCAINE FOLLOWING CHRONIC TREATMENT WITH GBR 12909.

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Chronic continuous cocaine infusion via osmotic minipump produces tolerance to both cocaine's behavioral effects and inhibition of dopamine uptake, but does not affect dopamine transporter binding. Continuous infusions of the selective dopamine uptake inhibitors GBR 12909 and RTI-117 were used in the present study to determine if tolerance is produced through dopaminergic mechanisms. Osmotic minipumps containing either GBR 12909 (30 mg/kg/day; 10 µl/h), RTI-117 (3.62 mg/kg/day) or saline (10 µl/h) were implanted into male Sprague-Dawley rats. Rats were placed in activity monitors for one hour each day. Pumps were removed after seven days and, twenty-four hours later, the GBR-treated rats were sacrificed and the caudate putamen and nucleus accumbens tissues prepared for determination of either [^{3}H]WIN 35,428 binding or [^{3}H]dopamine uptake in the presence of cocaine. Rats treated with GBR 12909 or RTI-117 exhibited significant increases in locomotion compared to saline, followed by partial tolerance. Behavioral tolerance developed at different rates for the dopamine uptake inhibitors, and cocaine. GBR 12909 produced tolerance to cocaine's inhibition of [^{3}H]dopamine uptake and a decrease in basal uptake of dopamine in the caudate putamen, but not in the nucleus accumbens. GBR 12909 decreased [^{3}H]WIN 35,428 binding affinity and the number of dopamine transporter binding sites by 57% in the nucleus accumbens, and 30% in the caudate putamen. These findings indicate that the selective dopamine uptake inhibitors differ from cocaine behaviorally, in the temporal pattern of locomotor activity, and neurochemically, as evidenced by selective changes in dopamine uptake and decreases in transporter number and binding affinity. The findings suggest the caudate putamen is more sensitive to changes in dopamine uptake, following selective dopamine uptake inhibition, than is the nucleus accumbens, perhaps due to the higher density of dopaminergic neurons in the caudate.

N-SUBSTITUTED-4',4"-DIFLUORO-3 α-(DIPHENYLMETHOXY)TROPANE ANALOGS: POTENT AND SELECTIVE DOPAMINE UPTAKE INHIBITORS

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A series of 4'- and 4',4"-substituted benztropine analogs has been prepared that functioned as dopamine uptake inhibitors, but did not produce cocaine-like behavior. Although these were selective at the dopamine transporter over the norepinephrine and serotonin transporters, they also demonstrated high affinity for muscarinic m_1 receptors. The most potent and selective compound in the initial series was 4',4"-difluoro-3α-(diphenylmethoxy) tropane. Interestingly, the 4',4"-difluoro-3α-diphenyhnethoxy moiety appears in another series of potent dopamine uptake inhibitors, eg. GBR-12909 which does not bind with high affinity to muscarinic receptors. Potentially, a separation of binding affinities for the dopamine transporter vs. muscarinic m_1 receptors would be achievable by substitution of the N-methyl group with other N-alkyl or alkylaryl substituents (eg. n-butyl, allyl, benzyl, propylphenyl, etc.). The N-substituted compounds were prepared from N-nor-4',4"-difluoro-3α-(diphenylmethoxy)tropane via acylation followed by hydride reduction of the amide or by direct alkylation. All the compounds bound to the dopamine transporter, radiolabeled with [^{3}H]WIN 35,428 (K_i range=8.5-2300 nM), and blocked dopamine reuptake (IC_{50} range=10-5400 nM) in rat caudate putamen. None of the compounds demonstrated high binding affinity at norepinephrine or serotonin transporters and several of the analogs demonstrated significantly (500-2000 fold) lower binding affinities at muscarinic m_1 receptors than the parent drug, benztropine. Therefore, these compounds will provide important tools with which to study the relationship between dopamine transporter binding, inhibition of doparnine uptake and psychomotor stimulant behavior.

N-SUBSTITUTED-4',4"-DIFLUORO-3 α-(DIPHENYLMETHOXY)TROPANE ANALOGS: BEHAVIORAL EFFECTS

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In previous studies (Newman et al, *J Med Chem* 37:2258, 1994, 38:3933, 1995) we examined benztropine analogs that have affinity for the dopamine transporter (DAT) and inhibit DA uptake. Despite these *in vitro* actions, the drugs generally did not have behavioral effects like cocaine. The present study examined several newly synthesized analogs based on the most potent and selective compound in the initial series. That compound [AHN 1-055, 4',4"difluoro-3α-(diphenylmethoxy)trope] had 11.8 nM affinity for the DAT, and greater than 700- and 200-fold selectivity for the DA over NE and 5-HT transporters, respectively. Although AHN 1-055 was selective among the transporters, it also had high affinity (6.1 nM) for muscarinic m_1 receptors. In the present study, the N-methyl group of AHN 1-055 was removed or replaced with various alkyl and arylalkyl substituents in an attempt to achieve selectivity for the DAT over m_1 receptors (see Agoston et al., CPDD 1996). All the compounds bound to the dopamine transporter (K_i values 11-2300 nM) and blocked DA uptake with selectivity over other transporters. Several had lower affinity at m_1 receptors than AHN 1-055. Both cocaine and AHN 1-055 increased locomotor activity in mice, whereas the other compounds were not efficacious. AHN 1-055 partially substituted in rats discriminating cocaine (10 mg/kg, i.p.) from saline, whereas the phenyltropane analog of cocaine, WIN 35,428, fully substituted. None of the other compounds produced any substitution across the range of behaviorally active doses. One explanation for the lack of cocaine-like effects of these drugs is that they were masked by prepotent antimuscarinic effects. However, cocaine-like effects were not obtained with compounds having no selectivity to ones with 20-fold selectivity for the DAT over m_1 receptors. These results demonstrate that activity at the DAT does not invariably result in cocaine-like behavioral effects, and that there may be more than one mode of interaction of drugs with the DAT. Finally, these compounds may provide leads for the discovery of medical treatments of cocaine abuse.

EFFECTS OF DOPAMINE ANTAGONISTS ON COCAINE and FOOD-MAINTAINED RESPONDING IN RHESUS MONKEYS

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Previous studies have suggested a prominent role for dopamine (DA) in the reinforcing effects of cocaine, because DA antagonists increase cocaine-maintained responding in a manner similar to decreasing the unit dose of cocaine. In order to extend our understanding of these effects, three DA antagonists (SCH23390, pimozide, and chlorpromazine) and a functional agonist (the cocaine analog, CFT) were studied on responding maintained under a multiple fixed-ratio (FR) 30 food, FR30 cocaine (1-100 µg/kg per injection), TO 10-min schedule in two different groups of four rhesus monkeys each. The effects of each drug depended upon the unit dose of cocaine. At intermediate (10 µg/kg per injection) unit doses antagonists decreased rates of responding maintained by either event in a dose-related manner. At higher (56-100 µg/kg per injection) unit doses antagonists increased and then decreased both food- and cocaine-maintained responding in a dose-related manner. These increases appeared to result from the blockade of non-specific rate-decreasing effects of self-administered cocaine, questioning their relevance to the reinforcing effects of cocaine. The results also failed to support a selective role for either D_1 or D_2 receptors in these effects. In contrast, CFT decreased cocaine-maintained responding at doses less than those that decreased food-maintained responding, and failed to shift the cocaine dose-effect to the left. These results suggest that agonists will be more effective than antagonists in developing pharmacological approaches to selectively decrease drug-seeking behavior. (Supported by IAG RA ND 95 24 and RO1 DA 09820).

EFFECTS OF TIME-OUT DURATION ON 2-ß-PROPANOYL-30-(4-TOLYL)-TROPANE (PTT) SELF-ADMINISTRATION IN MONKEYS.

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2-ß-propanoyl-3ß-(4-tolyl)-tropane (PTT) is a cocaine analog which has been shown to be 20 times more potent at binding the dopamine transporter compared to (-)cocaine. In drug discrimination studies cocaine generalizes to PTT. However, in self-administration studies, PTT functioned as a weak reinforcer when substituted for cocaine in rhesus monkeys responding under a fixed-interval 5-min schedule. The purpose of the present study was to evaluate the reinforcing effects of PTT under a fixed-ratio (FR) schedule to determine if decreasing the inter-injection interval would enhance the reinforcing effects of PTT. Male rhesus monkeys (N=3) were trained to respond under a multiple FR 30 food-drug-food schedule. Food (1g pellets) components were 30 min and cocaine (0.03 mg/kg/inj, i.v.) was available for 60 min; a 180-sec time-out (TO) followed each drug injection and a 15 min TO separated components. PTT (0.003-0.03 mg/kg/inj, i.v.) was substituted for cocaine for at least five sessions during the drug component and until stable responding was maintained, after which the TO following injections was reduced from 180 to 10 seconds. PTT maintained low rates of responding ,md substantially lower number of injections per session compared to cocaine. Decreasing the TO from 180-sec to 10-sec did not increase PTT-maintained responding or total session intake. At high PTT doses, responding in the second food component was nearly eliminated, indicating that monkeys were self-administering behaviorally-active doses. These results provide further evidence that PIT may have a low abuse liability.

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SEROTONERGIC MODULATION OF COCAINE'S DISCRIMINATIVE EFFECTS IN SQUIRREL MONKEYS

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Squirrel monkeys were trained to discriminate 0.3 mg/kg (N=4) or 1.0 mg/kg (N=4) cocaine and saline under a two-lever choice procedure in which responding on one lever was reinforced on an FR 30 schedule of food delivery when cocaine was administered ten minute before sessions, and responding on the other lever was reinforced when saline was administered. Substitution with a range of cocaine doses (0.03-1.0 mg/kg) occasioned dose-dependent increases in cocaine-lever responding. When administered alone, the non-selective serotonin agonist, quipazine, also occasioned dose-dependent increases in cocaine-lever responding. When administered in combination with cocaine, quipazine produced a leftward shift in the cocaine dose-effect curve, indicating an additive effect. The serotonin uptake inhibitor, fluoxetine, primarily occasioned saline-lever responding when administered alone, but enhanced the discriminative effects of cocaine in subjects trained at the lower cocaine dose. The $5HT_2$-selective antagonist, ketanserin, did not occasion cocaine-lever responding when administered alone, and it attenuated the discrminative effects of cocaine in most subjects. These results indicate that direct- and indirect-acting serotonin agonists can enhance the discriminative effects of, or possibly share stimulus properties with, cocaine, while serotonin antagonists can attenuate the discriminative effects of cocaine.

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PHARMACOLOGICAL ANTAGONISM OF A DISCRIMINATIVE STIMULUS PRODUCED BY A MIXTURE OF PHENTERMINE AND FENFLURAMINE 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). We have previously reported on drug discrimination experiments that have shown a combination of phentermine and fenfluramine can serve as a discriminative stimulus (DS) in rats. Furthermore, cross-generalisation studies revealed the stimulus produced by the mixture was not novel, rather these two aminergics interacted additively (Shoaib *et al.* 1995). The aim of the present experiment was to explore further the contribution of each amine in the mixture using pharmacological antagonists. Haloperidol (0.05-1.0 mg/kg IP) and methysergide (1.0-30.0 mg/kg IP) were employed as 'blanket' drugs to antagonise the PHEN and FEN DS properties respectively. Three groups of Sprague Dawely rats were trained to discriminate saline from (1) PHEN (2.0 mg/kg, IP), (2) FEN (2.0 mg/kg, IP) and the mixture PHEN+FEN (1.0 mg/kg of each, IP). Haloperidol dose-dependently antagonised the PHEN cue without affecting the FEN DS. Similarly, methysergide blocked selectively the FEN cue without affecting the PHEN DS. These antagonists failed to generalise for any DS in all three groups. Interestingly, in mixture-trained rats, only partial blockade of the DS was observed with each antagonist at doses that effectively blocked the individual components of the mixture. Complete antagonism of the mixture DS was evident only when both antagonists were administered together. These results suggest that both components of the drug mixture contribute equally toward the DS. Therefore, as revealed from previous generalisation tests, the present data confirm the additive nature of the drug mixture DS, indicating the importance of dual stimulation of both dopamine and serotonin in the treatment of certain addictions.

THE COCAINE-SENSITIVE NEURONAL 5-HT TRANSPORTER IS REGULATED BY GLYCOSYLATION

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It is known that cocaine inhibits neuronal serotonin (5-HT) transporter activity. However, little is known about whether cocaine modifies the cellular regulation of the 5-HT transporter. We first examined the role of N-linked glycosylation on 5-HT transporter activity in synaptosomes and nerve terminal membrane vesicles (NTMV). Next, we examined whether cocaine administration during pregnancy alters 5-HT transporter glycosylation in female rats or their offspring. Incubation of synaptosomes with the enzyme glycopeptidase F (40 U/ml, 30 min at 37°C) significantly increased the Km for ^{3}H-5-HT uptake from 48.5 ± 4.7 nM (control) to 248.2 ± 25.5 nM (glyco F-treated). No significant change in Vmax was seen. Experiments carried out in NTMV yielded similar results (Km for ^{3}H-5-HT uptake of 19.1 ± 1.7 nM and 60.0 ± 6.8 nM, for control- and glyco F-treated, respectively). Immunoblotting experiments using a 5-HT transporter antibody showed that the molecular weight of the 5-HT transporter in glyco F-treated synaptosomes was reduced (from 73 kDa MW to 63 kDa MW), consistent with its being de-glycosylated. Interestingly, glyco F treatment did not alter the kinetics of ^{3}H-paroxetine binding to the 5-HT transporter of synaptosomal membranes. These results indicate that cleavage of N-linked oligosaccharides reduces 5-HT transporter activity, although radioligand binding remains unaltered. To determine whether cocaine impairs 5-HT transporter glycosylation, midbrain from pregnant female rats treated with cocaine (15 mg/kg, b.i.d. 8 days) or vehicle were immunoblotted to determine whether reduced molecular weight (i.e. de-glycosylated) 5-HT transporter was present. No lower molecular weight transporter species (*e.g.* 63 kDa) were found. Likewise no lower molecular weight transporter species were seen brains of male offspring from cocaine-treated dams. Taken together these data suggest that alteration of 5-HT transporter glycosylation, although significant to transporter function, does not contribute to the functional changes in 5-HT neurotransmission seen following cocaine use or in the offspring of cocaine users.
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PHENTERMINE AND COCAINE DO NOT AFFECT FENFLURAMINE-INDUCED DEPLETION OF SEROTONIN IN MOUSE BRAIN

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Combined administration of phentermine and fenflurainine (PHEN/FEN) has been used as a treatment for cocaine dependence. It is well known that fenfluramine depletes brain serotonin (5-HT) in rodents, and the neurotoxic potential of PHEN/FEN has not been examined. We evaluated the effect of phentermine on fenfluramine-induced 5-HT depletion in mouse forebrain. In addition, the effect of PHEN/FEN on forebrain 5-HT was examined in the presence or absence of concurrent cocaine administration. In all experiments, the dosing regimen consisted of two injection sessions per day for four days. Mice were decapitated two weeks later and forebrain tissue levels of NE, DA and 5-HT were measured by HPLC-EC, Fenfluratnine (3, 10, 30 mg/kg, sc dose-dependently reduced forebrain 5-HT, and phentennine coadministration (7 mg/kg, sc) did not alter this effect. Cocaine (10 mg/kg, ip) given 60 min before or 60 min after PIIEN/FEN failed to modify PffEN/FEN-induced 5-HT depletion. The results show that phentermine and cocaine do not affect the long-term neurochemical actions of fenfluramine in mice. However, the clinical relevance of such findings remains to be determined.

WITHDRAWAL FROM COCAINE REDUCES THE OXYTOCIN RESPONSE TO 5-$HT_{2A/2C}$ AGONISTS.

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Hormone responses to challenges with specific 5-HT agonists provide useful peripheral indicators of the functional status of 5-HT receptors in the hypothalamus. Cocaine withdrawal potentiates the ACTH and prolactin responses to 5-$HT_{2A/2C}$ agonists. These responses may reflect sensitization of 5-HT, receptors. Oxytocin is directly secreted into the circulation from nerve terminals in the hypophysial neural lobe whose perikarya originate in the hypothalamus. Therefore, oxytocin is a direct and sensitive indicator of changes occurring in the hypothalamus. The oxytocin response to 5-HT, agonists was examined to determine if withdrawal from cocaine would alter the sensitivity of 5-HT, receptors in the hypothalamus. Cocaine (5 or 15 mg/kg bid) or saline was injected daily for 7 days. Three 5-HT, agonists were injected to rats 42 hours after the last cocaine injection: the 5-$HT_{2A/2C}$ agonist DOI (0.5-10 mg/kg ip), and the less selective 5-HT_{2C} agonists m-CPP (1-10 mg/kg ip) and MK-212 (1-10 mg/kg ip). Withdrawal from cocaine reduced the oxytocin response to all three 5-HT, agonists. The most dramatic reduction was seen with the maximal doses of these 5-HT, agonists, suggesting a reduction in the amount of oxytocin available to be released, rather than decreased sensitivity of 5-HT, receptors. These observations are consistent with Samyai *et al* (1992) who have observed a reduction in the hypothalamic concentration of oxytocin, after 4 days of cocaine exposure.

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EFFECTS OF REPEATED COCAINE ADMINISTRATION ON FENFLURAMINE-INDUCED ENDOCRINE RESPONSES IN HUMAN DRUG USERS

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Preclinical evidence indicates that withdrawal from chronic cocaine alters central serotonin (5-HT) function. In the present study, we examined 5-HT responsiveness in human substance users (N=8) who self-administerd intranasal cocaine in an in-patient research setting. Subjects participated in two daily self-administration sessions for five consecutive days; both cocaine (96 mg) and placebo (4 mg cocaine) were presented each day in a randomized double-blind fashion. Neuroendocrine challenge tests were performed using the 5-HT releasing agent fenfluramine (80 mg, po) five days before, and three days after, the repeated cocaine regimen. Blood samples were withdrawn at 30 min intervals for five hours after fenfluramine dosing, and plasma prolactin and cortisol were determined by RIA. Prolactin responses evoked by fenfluramine were not affected by prior cocaine exposure. Fenfluramine-induced cortisol responses, however, were significantly blunted during withdrawal from cocaine self-administration ($P<0.05$). Our preliminary data suggest that cocaine withdrawal in humans may be accompanied by 5-HT dysfunction. Further studies examining 5-HT responsiveness in human cocaine addicts are warranted.

COCAINE DELIRIUM AND CHOLINERGIC DEFICITS: IMPLICATIONS FOR A DYSREGULATION OF DA/ACH

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A case series of cocaine overdose victims who died following a syndrome of excited delirium (ED) was first described in Dade County, Florida in 1985. We have previously demonstrated that there is an apparent defect in the upregulation of dopamine (DA) transporter densities in the ED subgroup of cocaine overdose deaths. This lack of a compensatory increase in the DA transporter may indicate a diminished capacity for DA reuptake during a cocaine "binge". Chronic elevations in synaptic levels of DA may lead also to regulatory adaptations of postsynaptic cholinergic target neurons that receive DAergic inputs, thereby contributing to the adverse physiological and behavioral effects of cocaine. We have measured the activities of choline acetyltransferase (ChAT), the enzyme responsible for the synthesis of acetylcholine (ACh) in the human putamen using the radiochemical method of Fonnum. A significant decrease in ChAT activity was observed in the ED subgroup of cocaine overdose victims (79.2 ± 20.2 nmol/mg protein/hr; n = 13) as compared to drug-free and age-matched control subjects (134.0 ± 11.9 nmol/mg/hr; n = 11; $p < 0.005$). In contrast, cocaine overdose victims without preterminal psychosis had ChAT activities that were in the normal range (111.6 ± 12.2 nmol/mg/hr; n = 11). These studies provide neurochemical evidence for a dysregulation in the balance of striatal DA and ACh signaling in victims of excited delirium and sudden death. We suggest that altered striatal DAergic signaling which is exacerbated by a cholinergic deficit may precipitate the acute onset of excited delirium.

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ASSESSING DOPAMINERGIC NEURONAL INTEGRITY IN HUMAN COCAINE OVERDOSE VICTIMS.

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The reinforcing effects of cocaine have been linked to an increase in CNS dopamine (DA) neurotransmission resulting from the blockade of DA reuptake and mediated by the activation of DA receptors. DAergic signaling depends on a balance between DA reuptake by the synaptic membrane transporter and the rate of inactivation or removal from the cytoplasm by the synaptic vesicle monoamine transporter. In addition, cytoplasmic DA levels are controlled by monoamine oxidase and synaptic DA levels are regulated by catechol-O-methyl transferase. Radioligand binding to sites associated with monoamine-containing synaptic vesicles provides a novel approach for mapping the integrity of monoaminergic nerve terminals. The present study used the novel radioligand [^{125}1]-iodovinyltetrabenazine ([^{125}1]-TBZ) as a probe to assess the effects of chronic cocaine use on the status of the vesicular monoamine transporter as a marker of DAergic neuronal integrity **in** cocaine overdose victims. The tissue levels of DA and its metabolites (DOPAC and HVA) were assayed in parallel. Saturation binding of [^{125}1]-TBZ in striatal membranes revealed a single high affinity site (KD= 2.3 ± 0.9 nM and Bmax = 55.5 +/- 8.1 pmol/g tissue; n = 4) with a pharmacological profile (tetrabenazine > ketanscrin ≥ reserpine > haloperidol > GBR 12909 = fluoxetine > citalopram) consistent with **the specific** labeling of the vesicular monoamine transporter. Visualization of [^{125}1]-TBZ binding in human **brain** revealed intense labeling throughout the rostro-caudal extent of the striatum consistent **with** the known innervation of DAergic nerve terminals. Quantitative *in vitro* autoradiography of [^{125}1]-TBZ labeling demonstrated no significant alteration in the density of binding sites on monoamine synaptic vesicles in the striatum of cocaine overdose victims as compared to drug-free and age-matched control subjects. Quantitation of brain tissue levels of DA and its metabolites (DOPAC and HVA) demonstrated no significant difference across cocaine overdose groups. Taken together, these **findings** confirm the lack of neurochemical toxicity to DAergic neurons with chronic cocaine use.

EVALUATION OF THE EFFECTS OF VOLATILE ANESTHETICS IN MICE USING A FUNCTIONAL OBSERVATIONAL BATTERY

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Abused inhalants and volatile anesthetics may produce acute behavioral effects similar to those observed with acute ethanol and barbiturate administration. In an attempt to further characterize the effects of anesthetic exposure, the acute neurobehavioral effects of three volatile anesthetics (desflurane, enflurane and isoflurane) were investigated after 20 min inhalation exposures in mice using locomotor activity and a functional observational battery (FOB). The profiles of acute effects produced by desflurane (1,000-32,000 ppm), enflurane (1,000-12,000 ppm) and isoflurane (1,000-8,000 ppm) were similar to one another. All three inhalants produced concentration-dependent decreases in locomotor activity. The profile of effects for all three anesthetics on the FOB included changes in posture, decreased arousal, disturbances in gait, delayed righting reflexes and decreased sensorimotor reactivity. Recovery from the acute effects of these compounds was rapid and began within minutes of removal from the exposure chamber. The anesthetics produced a profile of neurobehavioral effects that was similar to that reported previously for ethanol, pentobarbital and for other abused solvents (*i.e.,* toluene and 1,1,1-trichlorethane) suggesting that these anesthetics may have similar behavioral abuse potential of the CNS depressant type.

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EVALUATION OF PERGOLIDE ON COCAINE SELF-ADMINISTRATION BY HUMANS

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Clinical evidence suggests that pergolide, a DI and D2 dopamine receptor agonist, may be useful in maintaining cocaine abstinence. We investigated pergolide's effects in a laboratory model of intravenous cocaine self-administration by humans. Ten inpatient volunteers (7M, 3F), averaging $185/wk on intravenous and smoked cocaine, received pergolide (0.05 mg bid) and placebo for eight days, with drug order balanced across subjects. Self-administration sessions followed four days of maintenance on each medication. A progressive ratio choice procedure (0, 8, 16, 32 mg/70 kg cocaine vs. $5) was utilized, with sessions consisting of: (a) **2** sample trials, where participants responded to receive the dose and money available that day, and (b) 5 choice trials, where participants chose between the available dose and money. Following each choice, the response requirement for the chosen option increased by 400, while the response requirement for the non-chosen option did not change. Cardiovascular measures occurred every **2** min, and subjective effects were measured 4 min after each reinforcer delivery. Cocaine dose-dependently increased self-administration, "craving," subjective effects, and cardiovascular measures. Women tended to self-administer more cocaine, and were less sensitive to its effects on systolic pressure and subjective measures (*e.g.,*"High"). Pergolide did not alter the reinforcing effects of cocaine, but increased systolic pressure and "craving" for cocaine. These data suggest that pergolide is not an effective treatment medication for cocaine abuse. Further, the efficacy of potential treatment medications needs to be determined for both men and women, since sensitivity to a range of cocaine's behavioral effects appears to be sexually dimorphic.

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EFFECTS OF ISOPARAFFINS ON MOTOR ACTIVITY

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The widespread abuse of solvents which are found in many industrial and consumer products has prompted the development of alternative solvents. One of the newer class of compounds, the isoparaffinic hydrocarbons, has recently been advertised as lacking abuse potential. The purpose of the present investigation was to evaluate four isoparaffins (ISOPAR C, E, G, H) for their effects on locomotor activity in mice. Classically abused solvents typically produce a biphasic effect with increases in locomotor activity at low concentrations and decreases at higher concentrations, effects also seen with abused depressant drugs. Test sessions lasting 30 min. took place daily in static exposure chambers with solvent exposures occurring twice a week (Tuesday & Friday). Isopar C and E (1000-6000 ppm) were quite volatile and produced only increased motor activity before reaching toxic concentrations. Isopar G (1000-6000 ppm) and H (500-2000 ppm) produced only minimal increases in locomotor activity, even at the highest concentrations examined. Neither behavioral profile for the ISOPARs resembles the typical biphasic effects observed for previously studied abused solvents. These results suggest that the ISOPARs may produce qualitatively different acute effects from abused solvents.

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DOPAMINERGIC MODULATION OF BARBITURATE-INDUCED CNS DEPRESSANT EFFECTS

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The effects of cocaine, a dopamine re-uptake transport inhibitor, and selective D_1 and D_2 receptor agonists and antagonists on pentobarbital (PB)-induced depression in male ICR mice was evaluated by measuring loss of righting reflex (LRR) and spontaneous locomotor (SLA). An n=6 was used for all control and treatment groups to systematically evaluate the effects of the D_1 and D_2 receptor ligands. All animals were injected by the IP route of administration with 50 mg/kg of PB for LRR studies, and experimental groups received subcutaneous injections of treatment drugs while controls received saline vehicle. All doses of the experimental drugs were chosen as ED_{50} values, or fractions thereof, obtained from the literature. Surprisingly, cocaine increased PB-induced LRR. Duration of LRR was also increased from control values by the D_2 agonist bromocriptine and the D_1 antagonist SCH-23390. Conversely, duration of LRR was reduced from control values by the D_1 agonist SKF-38393 and the D_2 antagonist spiperone. Additionally, we conducted studies to determine ED_{50} values for PB-induction of LRR in the presence of cocaine and various D_1 and D_2 receptor ligands. Cocaine reduced the ED_{50} value for PB-induced LRR, while the D_1 agonist SKF-21987 increased the ED_{50} value for PB-induced LRR. SLA experiments revealed similiar results. Our data demonstrate that dopaminergic modulation of the CNS depressant effects of PB occurs through both D_1 and D_2 receptor activation. With D_2 activation enhancing the depressant activity of PB and D_1 activation reducing it.

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CONTEXT AND REVERSAL LEARNING: INTERACTION IN A DRUG DISCRIMINATION TASK

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Drug discrimination learning is the process whereby one or more drugs acquire differential control over behavior. Training is done in much the same way as when studying more conventional, exteroceptive stimulus control of behavior. However, only limited work has been devoted to the interaction of these two classes of stimuli. To further investigate the commonalties and interaction between the two classes of stimuli, we examined contextual stimuli and reversal of drug discrimination behavior using four groups of rats: two groups were reversal-trained in the same context as for the original training; and, for the other groups, a contextual change was introduced in the reversal phase. The drug stimulus was pentobarbital (PB), either 10 or 17.5 mg/kg. A T-maze procedure was used and the exteroceptive context was the presence and absence of light in the experimental room. The speed of original training and the pre-reversal drug-dose generalization gradients were as described previously in the literature and did not differ between the sub-groups. Reversal learning took longer for all groups as compared to the original training. However, the low-dose group (PB 10 mg/kg) subjected to a contextual change during reversal acquisition mastered the reversal faster than the Low-dose group not experiencing a contextual change. Incorrect responding during PB sessions seemed mainly responsible for the slower acquisition in the reversal phase. When tested after reversal in the original training context, dose-generalization gradients were affected differentially depending upon the conditioning history of the animals: dose generalization to the training stimulus in the high-dose condition was reduced for animals experiencing a context change during reversal training, but not for PB 17.5 mg/kg animals not experiencing a contextual change. Such differential effects did not occur in the low-dose condition. Thus, drug stimuli and contextual stimuli interact in the control of behavior. Supported in part by NIDA grant KO2 DA00253.

ATTENUATION OF THE BEHAVIORAL EFFECTS OF ANXIOLYTICS BY THE K-CHANNEL BLOCKER 4-AMINOPYRIDINE

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In the present study, the anxiolytic-like effects of the benzodiazepine chlordiazepoxide (CDP), the sedative pentobarbital, and the SHT1A agonist buspirone were evaluated alone and after pretreatment with the voltage-dependent potassium channel blocker 4-aminopyridine (4-AP) in pigeons responding under a "conflict" schedule. Under this schedule, completion of an FR30 in the presence of a white key resulted in 3-sec access to mixed grain and completion of an FR30 in the presence of a red key resulted in 3-sec access to mixed grain and a mild electric shock (punished responding; 1-3 mA, 200 msec). CDP (3.0 - 17.8 mg/kg), pentobarbital (3.0 - 17.8 mg/kg) and buspirone (0.1 - 3.0 mg/kg) produced dosedependent increases in punished responding at doses that did not effect or decreased unpunished responding. Pretreatment with 4-AP (0.1 - 1.0 mg/kg) attenuated the increases in punished responding to approximately baseline levels and had no effect on unpunished responding in five of six pigeons treated with CDP, in four of five pigeons treated with pentobarbital and in three of six pigeons treated with buspirone. In a second study, rats were trained to discriminate 3.0 mg/kg of chlordiazepoxide from saline using a 2-lever drug discrimination procedure. Completion of an FR30 on the injection-appropriate lever resulted in the delivery of a food pellet reinforcer. When administered alone, chlordiazepoxide (0.1 - 5.6 mg/kg) produced dose-dependent increases in responding on the CDP-associated lever. Pretreatment with 4-AP (1 mg/kg) produced a rightward shift of the CDP dose-response curve. Taken together, the present results suggest that voltage-dependent K-channels may be involved in the behavioral effects of anxiolytics.

EFFECTS OF TRIAZOLAM AND IMIDAZENIL UNDER DIFFERENT LEARNING CONDITIONS IN SQUIRREL MONKEYS

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Although animal and human studies have shown that benzodiazepine receptor agonists disrupt learning and memory, several reports suggest that these drugs can improve performance in anxious subjects. Therefore, we examined the effects of triazolam and imidazenil on acquisition (learning) under two different learning conditions in squirrel monkeys. Responding was maintained by food presentation under a repeated acquisition of behavioral chains procedure. Learning was studied under two different conditions: 1) a chain schedule that maintained low error levels and rapid acquisition and 2) a chain schedule with concurrent noncontingent tail-shock presentation that maintained high error levels and slowed acquisition. Under both schedules, subjects acquired a different three-response sequence each session, and sequence completions were reinforced under a fixed-ratio FR 5 schedule. Errors produced a brief timeout. Under the non-shock chain schedule, triazolam (0.0056 - 0.1 mg/kg) dose-dependently decreased response rate and increased percent errors. Imidazenil (0.032 - 1 mg/kg) had little or no effect on either response rate or percent errors. When administered in combination, imidazenil (0.1 mg/kg) antagonized both the rate-decreasing and error-increasing effects of triazolam. In contrast to the error-increasing effects produced under the non-shock chain schedule, under the chain schedule with noncontingent tail-shock presentation, triazolam (0.0018 - 0.1 mg/kg) decreased errors and enhanced acquisition. Imidazenil (0.001 - 1 mg/kg) also produced error-decreasing effects under this condition but did not decrease response rate. These data suggest that the effects of benzodiazepine agonists on learning are determined, in part, by the conditions maintaining acquisition. The data further suggest that the effects of full and partial agonists can differ under these conditions.
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MIDAZOLAM AND ALFENTANIL SELF-INJECTION IN BABOONS

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Self-injection of the benzodiazepine agonist, midazolam (MDZ), was compared with the opioid agonist, alfentanil (ALF), under limited-access (2 hr/day) conditions. Baboons with chronic intravenous catheters self-injected MDZ (n=3, 0.32 mg/kg/inj) or ALF (n=2, 0.0032 mg/kg/inj) under a low fixed-ratio (FR 3 or 10) schedule. MDZ was self-injected at intermediate rates (4-13 inj/session) compared to the higher rates (12-25 inj/session) of self-injection of ALF and to the very low rates of chronic saline self-injection (0-3 inj/session). Saline or different drug doses were substituted for single sessions. Saline substitution generally produced increases in self-injections. Preliminary data indicate that substitution of low doses of ALF (0.00032-0.01 mg/kg/inj) increased number of self-injections whereas the high dose (0.1mg/kg/inj) decreased self-injections. Low doses of MDZ (0.001-0.032 mg/kg/injection) also increased self-injections. Administration, 15 min. before experimental sessions, of the opioid antagonist, naloxone (0.00032-0.1 mg/kg, iv.) to the ALF baboons or the benzodiazepine antagonist, flumazenil (0.0032-0.1 mg/kg, iv.) to the MDZ baboons did not produce behavioral signs of withdrawal (e.g. tremor, bruxism, vomiting). Self-injection of ALF was increased by naloxone in a dosedependent manner. Flumazenil did not reliably increase MDZ self-injection. These data show that both ALF and MDZ served as intravenous reinforcers under conditions of limited drug access in baboons that were not physically dependent. Ongoing research will investigate the modulation of self-injection by physical dependence.

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"ROCHE" ABUSE ALONG THE TEXAS-MEXICO BORDER

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During the past three years, flunitrazepam (Rohypnol) has been increasingly abused in the US, most visibly in Florida and Texas. In December 1995 we interviewed 39 drug users along the Mexico border between Brownsville and Laredo who were referred to us as users of Rohypnol. The users included prisoners, junior- and high-school students, and adolescents in drug abuse treatment programs. The purpose of our research was to describe the varieties of Rohypnol abuse and to identify the public health and social consequences. We found that most users we interviewed were not specifically seeking Rohypnol; instead, they were seeking tablets imprinted with "Roche." Users' descriptions of tablets usually matched Rohypnol, or Rivotril (clonazepam), or Lexotán (bromazepam) or Valium (diazepam) that was marketed in Mexico. Most users thought that "Roche" was the name of the medication and that similarly marked, variously colored tablets with different numbers imprinted on them were different strengths of the same medication. Use of other pharmaceuticals was also reported. Most commonly, the tablets were taken orally, either alone or in combination with alcohol or marijuana. A few users reported crushing tablets and injecting or snorting them. Others smoked them, either alone or in a marijuana cigarette. Heroin addicts reported using them to self-medicate withdrawal symptoms. After ingesting 2 to 10 tablets, users often had anterograde amnesia. The main findings of the study including additional interviews conducted in Austin and Houston has been published (Calhoun *et al., 1996)*

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FLUNITRAZEPAM (ROHYPNOL) ABUSE IN AUSTIN, TEXAS: JUST ANOTHER BENZODIAZEPINE?

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As part of an investigation of flunitrazepam (FLU) abuse in Texas, we conducted, in the Austin area, brief interviews with 86 respondents, detailed interviews with 20 users, and discussions with local law enforcement personnel, drug treatment centers, and student health services. Of the 86 surveyed, 17 (20%) had used FLU, and an additional 12 (14%) were familiar with it. Three distinct groups of users became apparent: homeless youth, among whom FLU use was quite prevalent; heroin dependent persons; and college students, who typically reported episodic periods of use. FLU was perceived as being readily available, at a cost of zero to five dollars per 2 mg. tablet. Administration was predominately oral, although limited experimentation with smoking and intravenous injection was reported. Effects sought by users included euphoria, anxiolysis, hypnosis, relief of opiate withdrawal symptoms, amelioration of the crash from cocaine or MDMA, and amplification or replacement of the effects of alcohol. Adverse effects included anterograde amnesia, discoordination with resulting injuries, irritability, and two reports of respiratory arrest. Although the possibility of being sexually assaulted while under the influence of FLU was mentioned by many respondents, no specific examples were cited. These characteristics of FLU abuse, with the exception of unusual availability and popularity, resemble those previously reported for other benzodiazepines. The main findings of the study including additional interviews conducted in Houston and the Mexican border area has been published (Calhoun *et al.* 1996).

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RATE OF ONSET OF DRUG EFFECTS IN RELATION TO ITS ABUSE POTENTIAL: FLUNITRAZEPAM

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The rate of onset of effects may be related to drug abuse potential. Benzodiazepines with fast absorption and onset of effects might be preferred by drug abusers. The manipulation of rate of delivery could be a useful method to study differences in onset of effects. Nine male healthy volunteers participated in a randomized, double-blind, double-dummy, cross-over study. Drugs were administered in six capsules ingested at 30-min intervals over 2.5 h. Conditions were: placebo, flunitrazepam (FNZ) SLOW (six doses of 0.4 mg), and FNZ FAST (five doses of placebo and a single last dose of 2 mg). Variables included: vital signs, subjective effects (visual analog scales, ARCI, POMS), psychomotor performance (simple reaction time, DSST, Maddox wing) and blood samples. Compared to placebo, both flunitrazepam conditions decreased temperature and induced an impairment of performance tasks and sedative effects. The drug also produced increases in some scales related to pleasurable effects ("high", "good effects", "liking"). Comparison of peak measures between both FNZ conditions showed a general tendency to increased sedative effects under SLOW condition, while scores of pleasurable-related effects were slightly higher under FAST condition (no significant differences). Peak plasma concentrations were similar between both FNZ conditions. Results do not completely reproduce previous results with diazepam using similar methodology.

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PREDICTORS OF INDIVIDUAL DIFFERENCES IN ALPRAZOLAM SELF-MEDICATION

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Twenty-seven M,F patients with generalized anxiety or panic disorder participated in an outpatient study in which alprazolam (0.5mg) and placebo were available for self-medication "as needed". Patients were not drug abusers and many were relatively medication naive. Alprazolam and placebo were dispensed under double-blind conditions in color-coded capsules contained in electronic medication bottles which recorded the date and time of each bottle opening. After a one week sampling period of each drug/color combination, patients received both medication colors on each weekly visit so that they could choose whichever they preferred at any time. Measures of drug use included the amount of use, the percent of days that capsules were self-administered, and the alprazolam preference ratio (Alz/total). Patterns of medication use and observed medication effects indicated that patients were self-medicating and not abusing alprazolam. Alprazolam clearly was preferred over placebo in 23 out of 27 patients. Correlational analyses indicated that the four subjects with low alprazolam preference were less anxious, more extroverted, more aggressive, and had higher social self-efficacy than subjects who preferred the drug. Alprazolam was shown to be a reinforcer for 20 of the 27 subjects ($p < 0.05$ by binomial probability). Correlations between intake measures and medication use showed that lower tolerance for alcohol, less experience of problematic consequences of alcohol use, unemployment, less extroversion, and lower internal locus of control were predictive of greater alprazolam preference and use Frequency in both the full sample and in the subpopulation of subjects with showing statistically significant reinforcement. Levels of *intake* anxiety did not correlate with reinforcement, nor did they predict subsequent medication use in patients reinforced by alprazolam, but they did predict medication use in the full sample.

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A COMPARISON OF PRESCRIBED AND NON-PRESCRIBED BENZODIAZEPINE USERS IN METHADONE-MAINTAINED PATIENTS

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The authors targeted patients who tested positive for benzodiazepines more then three times in a month on their urine drug screens. 34 patients were singled out; 21 were prescribed benzodiazepines while the remaining 13 were not. Cocaine and alcohol usage was minima1 (two patients) in the target group with both groups comparing evenly. The groups were compared on symptoms based on addiction severity, depression, anxiety and psychoticism. To evaluate this, the Addiction Severity Index, the SCL-90 (Symptom Check List), Beck's Anxiety Scale and the Spielberger Scale were administered. On the ASI, the prescribed patients had higher average composite scores in alcohol, medical, employment, social, and psychiatric sections. Non prescription users had higher scores in drug and legal sections. On the SCL-90, the average scores of prescribed patients were higher then the other group in all parameters. On the Spielberger depression scale, the patients on prescription benzodiazepines had higher average raw scores than the other signifying higher depressive state and trait in the prescription group. On the Beck's Anxiety Scale patients on prescription benzodiazepines had higher average scores than the other reflecting more anxiety levels. Certain elements of these scales were analyzed with T-test and significance was confirmed.

ARE PATIENTS WITH IATROGENIC BENZODIAZEPINE DEPENDENCE "PSYCHOLOGICALLY DEPENDENT" OR "ADDICTED"?

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It has been suggested that iatrogenic BZ dependence is characterized mainly by physical dependence and that "psychological" dependence doesn't occur in therapeutic users. However, there is relatively little data on the psychological features of BZ dependence. We examined those psychological features in 24 patients dependent on prescribed BZs and enrolled in a discontinuation study. The most frequently endorsed DSM IV criteria (287.5% of patients) were BZ use in larger amounts/longer time than intended and persistent desire/ unsuccessful efforts to quit; 45.8% of patients met a DSM diagnosis without the physiological criteria involving tolerance or withdrawal. 58.3% of patients never had a period of successful BZ abstinence in their life history despite using BZs for an average of 7.9 yrs. During a gradual dose reduction on clonazepam under double-blind conditions, one third of the patients dropped out of the study; those individuals displayed expectancies at study intake indicating lower desires to quit, lesser confidence that they could stop medication or manage without it, and greater fears of going without BZ. All negative expectations were focused on a perceived need for medication and were not related to concerns about physiological withdrawal. As part of the study design, a subset of patients were instructed that they were beginning dose-reduction when dose actually was held constant. 50% of those instructed showed a rebound increase in anxiety revealing an important "expectational" component to the withdrawal syndrome. Finally, 70% of patients used additional doses of "emergency medication" and 64% of those increased use during clonazepam dose-reduction indicating a withdrawal-induced increase in medication use. Although most patients suffered from anxiety and expressed a self-medication motivation for continued BZ use, these data show that "psychological" features involving patient expectations and persistent self-administration behavior are involved in the maintenance of BZ dependence.

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CALCIUM CHANNEL BLOCKADE AND ALCOHOL WITHDRAWAL SYNDROME (AWS)

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Animal studies reveal that calcium channel blockers including verapamil reduce signs of AWS. A double-blind, double-dummy parallel study was conducted in 18 patients with acute AWS, as determined by elevated scores (>10) on a standardized withdrawal scale (CIWAr). Subjects received placebo-placebo, or 10 mg verapamil-placebo, or placebo-diazepam 10 mg. The first treatment was given intravenously (iv) over two mins followed by the second iv over five mins. Withdrawal scales, HR and BP were rated at regular intervals one hour pre and post drug administration. Plasma catecholamines were collected via Kowarski pump for 30 minutes pre and post drug administration, and measured by REA. Results revealed that for AUC change scores, all groups improved relative to baseline and catecholamines were unchanged. Significantly greater reductions ($p<0.05$) were detected for tremor and nausea with the positive control condition (diazepam). Even though the power of this study was low, the multiple and careful assessments provided indications of efficacy for diazepam. Only for systolic BP was there evidence that verapamil differed from placebo. In conclusion, at usual therapeutic doses iv verapamil appeared less effective than iv diazepam, and not substantially different from placebo.

SACCADIC EYE MOVEMENTS AS A RESEARCH TOOL IN HUMAN ADDICTION

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The measurement of saccadic eye movements (SEMs) is a sensitive measure of central drug effects. SEM parameters can be obtained quickly and repeatedly and the technique is acceptable to research subjects (see Coupland *et al* 1995). Changes in SEM parameters are evident following the administration of several classes of drugs of abuse (Glue 1991). The benzodiazepines when administered intravenously to volunteers, cause a dose-dependent decrease in peak saccade velocity, acceleration and deceleration, which are correlated with plasma benzodiazepine levels. Similarly, alcohol reduces saccade peak velocity and prolongs duration. Tolerance to these effects may develop in subjects who are dependent, in that the degree of benzodiazepine- or alcohol-induced slowing is reduced. Conversely, amphetamines abolish the usual "fatigue effect" commonly observed with repeated measures, and in higher doses may increase saccade velocity above baseline. Previous studies have shown that SEMs are sensitive to the effects of opioid ligands, such that methadone decreases saccade peak velocity. We have been using the SEM technique to explore the relationship of benzodiazepine and opioid tolerance to withdrawal. For instance, during a methadone-buprenorphine transfer we have shown that on day two of the transfer saccade peak velocity was significantly increased, possibly reflecting a clearance of methadone from central opioid receptors. These and other data on the potential use of SEMS in the study of addiction will be presented.

Coupland, N.J.; Marshall, R.W.; Wilson, S.J.; and Nutt, D.J. The use of saccadic eye movement measures in psychopharmacology. In: Hindmarch, I. and Stonier, P.D. eds. Human Psychopharmacology Vol 5. John Wiley & Sons Ltd, 1995, pp. 137-155.

Glue, P. The pharmacology of saccadic eye movements. J Psychopharmacol 1991, Vol 5, 377.387.

EFFECTS OF WORK REQUIREMENT AND NALTREXONE ON HUMAN ETHANOL SELF-ADMINISTRATION

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The effects of work requirement **(Study 1)** and 50 mg of naltrexone **(Study 2)** on human ethanol self-administration were systematically examined. Healthy volunteers with a history of alcohol consumption of 12 to 16 drinks per week were recruited as subjects. **Study 1:** Four subjects were permitted to self-administer 4% w/v, 8% w/v or 16% w/v ethanol solution contingent upon completing of a response requirement, fixed ratio (FR), of 32, 64, or 128 responses. Ethanol consumption at lower doses decreased with increases in FR. Ethanol consumption at the high dose was greatest across all work requirement conditions indicating the reinforcing effects of high dose ethanol. Ethanol consumption was sensitive to unit price with 51-82% of the variance explained by the unit price model. In **Study 2** the effects of placebo or 50 mg of naltrexone on ethanol consumption was examined. Placebo or 50 mg of naltrexone were administered 30 minutes prior to the self-administration trial. In a 60 minute trial six subjects were allowed to self-administer up to 100 deliveries of 8% w/v ethanol at 10 ml per delivery. Deliveries of ethanol or deionized water were contingent on completion of 64 button "A" or "B" presses. Naltrexone pre-treatment significantly decreased ethanol consumption in social drinkers relative to placebo. Naltrexone also decreased desire for alcohol, thoughts about alcohol, and willingness to buy alcohol.

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INFLUENCE OF REINFORCEMENT CONTINGENCIES ON THE BEHAVIORAL EFFECTS OF ALCOHOL IN HUMANS

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The effects of performance-contingent (piecework) vs. non-contingent (salary) payment schedules on the behavioral effects of alcohol and on dose choice were examined. Five healthy adult moderate alcohol users, blind to the study drug, gave written consent and participated five days per week over three consecutive weeks. Each day subjects completed a 3-hr session consisting of repeated presentations of performance tasks and visual-analog drug ratings, beginning 30 minutes after alcohol administration (0.0 or 1.0 g/l). A standard meal was consumed 60 minutes prior to dose administration. Subjects were exposed to four 3-day blocks, each consisting of two sampling days, during which the placebo and active doses were each administered, followed by a choice day, during which subjects chose between the placebo and active doses administered on the previous two sampling days. Piecework and salary payment schedules were each in effect during two of the four blocks and were presented in an alternating fashion. No differences in baseline performance were observed as a function of the payment schedules. Performance on all tasks was impaired and ratings of 'High' were increased by alcohol. With the exception of time estimation, these effects were similar during piecework and salary payment schedules. Differential effects of alcohol were observed as a function of payment schedules during the time estimation task, with significant dose-related decreases in estimation accuracy occurring during the piecework but not during the salary schedule. Dose-related performance impairment resulted in decreased session earnings when the piecework payment schedule was in effect, but not during the salary payment schedule. Despite the differential consequences associated with alcohol administration during piecework and salary payment schedules, no effects on dose choice were observed.

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EFFECTS OF ISRADIPINE ON THE SUBJECT-RATED AND PERFORMANCE-IMPAIRING EFFECTS OF ETHANOL IN HUMANS

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The acute cardiovascular, subject-rated and performance-impairing effects of ethanol (0 and 1.0 g/kg), alone and in combination with isradipine (0 and 30 mg), were examined in 6 moderate drinkers. Subjects received one of the four combinations during each of four sessions. Order of administration was quasi-random. Heart rate, blood pressure, subject-rated drug effects and performance were measured before ethanol and isradipine administration and periodically afterwards for five hours. Subjects completed an End-of-Day Questionnaire approximately five hours after ethanol administration that asked them to rate various aspects of the overall drug effect. Ethanol alone did not affect heart rate or blood pressure. Isradipine alone increased heart rate and decreased blood pressure. The ethanol-isradipine combination produced cardiovascular effects similar in magnitude to those observed with isradipine alone. Breath-alcohol concentrations were similar in magnitude when ethanol was administered alone or in combination with isradipinc, which suggests isradipine did not inhibit ethanol absorption. Ethanol alone increased subject ratings of "Drunk" throughout most of the experimental session relative to the placebo condition, and increased ratings of "Drug Liking" on the End-of-Day Questionnaire. Isradipine alone had no effect on these measures. Combining ethanol and isradipine decreased these ratings relative to the ethanol-alone condition, which suggests isradipine attenuated some of the subject-rated effects of ethanol. These findings are concordant with preclinical studies that examined the effects of isradipine on the reinforcing and discriminative stimulus effects of ethanol, and suggest calcium ions are involved in mediating the behavioral effects of ethanol in humans. Future studies should determine if isradipine alters other behavioral effects (*e.g.,* reinforcing or discriminative-stimulus effects) of ethanol in humans. Importantly, future studies should determine whether lower doses of isradipine attenuate the behavioral effects of ethanol since the pronounced cardiovascular effects of the high dose of isradipine tested in the present experiment would obviate its use as an adjunct in the treatment of ethanol abuse.

NALTREXONE ANTAGONIZES THE DISCRIMINATIVE STIMULUS PROPERTIES OF ETHANOL IN LEWIS RATS

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Naltrexone (NTX), an opioid antagonist, has shown treatment efficacy for alcoholism, confirming many preclinical studies demonstrating ethanol (EtOH) intake is reduced by opioid antagonists. This study extends these findings to demonstrate that NTX attenuates the discriminative stimulus effects of EtOH. Lewis rats (data based on 5-9 rats) were trained to discriminate EtOH (1.5 g/kg; 15% solution, i.g.) from water in a two-lever, food-reinforced (FR15) discrimination procedure (15 min session; 15 min pretreatment time). Once EtOH demonstrated control over behavior (6 consecutive days of >90% drug-appropriate responding), various tests were run: 1) substitution tests with EtOH (0.25-2.0 g/kg); 2) substitution tests with pentobarbital (3-18 mg/kg, i.p.; 20 min pretreatment time) and amphetamine (0.5-2.0 mg/kg, i.p.; 15 min pretreatment time); 3) combination tests of EtOH (1.5 g/kg) with naltrexone (3-30 mg/kg, s.c.; 5 min pretreatment time); 4) combination tests of EtOH (0.25-2.0 g/kg) with naltrexone (0, 3 and 10 mg/kg, s.c.); and 5) combination tests of EtOH (0, 0.25 and 0.5 g/kg) with morphine (0.32-5.6 mg/kg, s.c.; 30 min pretreatment time). Dose-related responding to EtOH was seen, and pentobarbital, but not amphetamine, substituted for EtOH. NTX attenuated EtOH (1.5 g/kg) responding in a dose-related manner with no effect on response rate. NTX (3 and 10 mg/kg) attenuated EtOH (0.25-2.0 g/kg) responding in a dose-related manner with some disruption of response rate. In contrast, morphine, an opioid agonist, failed to potentiate EtOH responding. Morphine did alter responding regardless of EtOH dose, but did not substitute for EtOH. Finally, NTX (10 mg/kg) had no effect on plasma EtOH (1.5 g/kg) concentrations from 5-120 min post-infusion. These data show that EtOH functions as a discriminative stimulus in Lewis rats and that NTX can partially antagonize these effects of EtOH. This extends previous research using EtOH intake procedures to drug discrimination which has the procedural advantage of control over EtOH dose.

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PENTOBARBITAL DISCRIMINATION UNDER CONCURRENT FIXED-INTERVAL SCHEDULES

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Pigeons were trained to discriminate between 5 mg/kg pentobarbital and saline under a concurrent fixed-interval 240 sec fixed-interval 60 sec schedule (conc FI FI), where the presence or absence of pentobarbital indicated which response key was associated with the shorter FI value. The pigeons learned the discrimination, making about 80% of their responses on the key associated with the FI 60 component after pentobarbital and about 70% after saline, which is close. to the values predicted by the matching law. Analysis of the cumulative response records showed that responding under the FI 60 component came under temporal control with a post reinforcement pause followed by increased responding. Responding under the FI 240 component was controlled by responding under the FI 60 component, with bursts of responding on the key associated with the FI 240 component occurring during post-reinforcement pauses in the FI 60 component. Substitution tests were conducted under conc 150 FI 150. After 1, 3, 5.6 and 10 mg/kg pentobarbital, 38, 65, 81, and 82% of the responses occurred on the pentobarbital key. These data show that drug discrimination can be established under conc FI schedules, that the distribution of responses across keys is close to that predicted by the matching law, that temporal control occurs under the shorter Ii schedule, and that graded dose-effect curves can be generated by the training drug.

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FLUVOXAMINE AND ETHANOL: BEHAVIORAL INTERACTIONS

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Serotonin reuptake inhibitors, *e.g.,* fluvoxamine, have been proposed for the treatment of a variety of substance abuse disorders, including alcoholism. A potential side-effect of any drug is that it potentiates the effects of ethanol. We examined the ability of fluvoxamine to potentiate the behavioral effects of ethanol. The effects of ethanol and fluvoxamine alone and in combination on the responding of rats under a fixed-ratio ten (FR10) schedule of food reinforcement were examined. Experimental sessions were 10 minutes long, and ethanol was given 10 minutes and fluvoxamine 30 minutes before the start of the session. Drugs were given ip. Sessions were signaled by a cue light over the response lever and white noise. Completion of 10 responses (FR10) resulted in food delivery, turning off the cue light and white noise, and turning on a houselight for 10 seconds. After 10 seconds, the houselight was turned off, and the cue light and white noise turned on and the FR 10 schedule was again in effect. Doses of ethanol greater than 0.4 g/kg and doses of fluvoxamine greater than 5.6 mg/kg reduced responding when given alone. When ethanol was combined with 1 or 3 mg/kg of fluvoxamine, the effects were similar to those of ethanol given alone or given in combination with saline. Ethanol doses that did not alter response-rate alone given in combination with 10 mg/kg fluvoxamine, produced effects similar to those seen with fluvoxamine alone. The effects of higher ethanol doses in combination with 10 mg/kg of fluvoxamine were similar to or less than those expected by simple addition of the effects of each drug. Thus, fluvoxamine and ethanol do not appear to produce synergistic effects.

STIMULUS PROPERTIES OF ETHANOL ARE NOT MEDIATED VIA 5-HT$_3$ RECEPTORS

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5-HT3 receptor antagonists have been reported to block the discriminative cue of ethanol, suggesting that some of the effects of ethanol are mediated by the 5-HT3 receptor complex. Data from neurophysiological, neurochemical and behavioral studies provide some support for this. If 5-HT3 antagonists can modify the reinforcing and discriminative properties of ethanol, one would expect that 5-HT3 agonists may exhibit some efficacy in mimicking behavioral effects of ethanol. The main purpose of the present study was to examine the effects of the 5-HT3 receptor agonist mCPBG in rats trained to discriminate ethanol from saline. The 5-HT3 receptor antagonists tropisetron and ondansetron were also tested for their ability to attenuate the stimulus properties of ethanol. Sixteen male Wistar rats were trained to discriminate ethanol (1.0 g/kg, i.p.) from saline. Lever pressing was maintained under fixed-ratio (FR 10) schedules of food reinforcement. mCPBG (0.1-10 mg/kg i.p. and 1-35 µg i.c.v.) could not substitute for ethanol at any dose and route of administration tested. Both tropisetron (0.001-1.0 mg/kg i.p.) and ondansetron (0.001-1.0 mg/kg) were unable to block ethanol discrimination. Since several different 5-HT3 antagonists also fail to alter the discriminative stimulus effects of cocaine, amphetamine, nicotine and morphine, the major conclusion that can be drawn from this and previous studies is that the 5-HT3 receptors do not appear to be primarily responsible for mediation of the stimulus properties of drugs of abuse.

EFFECTS OF DRUG TREATMENTS ON ETHANOL CONSUMPTION AND PREFERENCE IN ETHANOL-PREFERRING C57BL/6J MICE

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The CS7BL/6J inbred mouse exhibits a genetic predisposition for high ethanol preference that may be related to the central hypodopaminergic function observed in this strain. Based on this hypothesis, the aim of the present experiment was to investigate the effects of dopamine agonists on ethanol consumption and preference. SKF 38393, a D1, bromocriptine, a D2, and quinpirole, a D2/D3, dopamine agonists were studied. In addition, the effects of fluoxetine, a serotonin uptake inhibitor, and naltrexone, an opiate antagonist were also investigated. Mice were housed in groups of six per cage. They were offered tap water and an ethanol solution in a two-bottle free-choice procedure. The ethanol concentration was increased over about a month from 2 to 14% (v/v) and then maintained at 8% (v/v), a concentration that produced ethanol preference. The volumes of water and ethanol consumed were recorded every 24-h at 9:00 a.m. Drugs were administered intraperitoneally at 9:00 a.m. and 4:00 p.m. SKF 38393 (10-30 mg/kg) decreased ethanol preference as indicated by increasing water intake without changing total fluid drinking. In contrast, bromocriptine (30 mg/kg) and quinpirole (10 mg/kg) decreased ethanol intake without affecting preference. Fluoxetine (20 mg/kg) decreased ethanol preference at a dose that also decreased total fluid intake. Naltrexone did not affect ethanol preference at doses up to 30 mg/kg. To study further the effects of SKF 38393, a dose of 30 mg/kg was administered over a range of ethanol concentrations from 4 to 12%. SKF 38393 decreased ethanol preference at 8-12% and did not affect consumption at 4%. In conclusion, among the different compounds tested, only the D1 dopamine partial agonist decreased ethanol preference in C57BL/6J mice. Further studies are needed to compare dopamine agonists with different intrinsic activity and selectivity for dopamine receptor subtypes.

EFFECT OF CONCURRENT ALCOHOL AND ITS WITHDRAWAL ON BREAK POINTS IN RATS SELF-ADMINISTERING ALCOHOL ON A PROGRESSIVE RATIO SCHEDULE.

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There are few parametric data on a rigorous measure of motivation for orally self administered ethanol. Break points (BP) on an operant progressive ratio (PR) schedule have been used to investigate motivation for self-administration of psychostimulants. We therefore investigated BP on a PR schedule in individually housed hooded Lister rats, responding for orally available ethanol. Rats were trained using Samson's (1986) sucrose fading technique and BPs established across a range of concentrations of ethanol (0-20%). The BP was the ratio at which rats stopped responding for a period of time, two standard deviations greater than the mean inter-reinforcer-time on the FR4 training schedule (i.e., the ratio at which rats stopped responding for 30 minutes or more). The BP vs. concentration curve was an inverted U-shaped function which peaked at an ethanol concentration of 10% (BP16.6±2.3); at higher alcohol concentrations the BP declined although this was not statistically reliable. To study the effects of concurrent ethanol administration, 7% ethanol diet was given for nine days and the BP established using a reinforcer concentration of 5% (on the ascending limb of the BP vs. concentration curve). With a voluntary dietary ethanol intake of approx. 14g/kg/day, the BP declined from 11.1 ±1.8) to 4.9 (±1.2). Four (but not one) repeated cycles of dietary ethanol and withdrawal led to an increase in the BP during withdrawal, relative to controls. These data indicate that this measure of motivation for ethanol-reinforced responding is predictably sensitive to the effects of ethanol given freely in the diet, and that motivation for ethanol may increase with repeated withdrawal.

REFERENCE: Samson HH (1986). Alcohol: Clin Exp Res, 10: 436-442.
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DO DRUGS OF ABUSE DISRUPT WORKING MEMORY IN PIGEONS UNDER A MATCHING-TO-SAMPLE BASELINE?

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This laboratory and others have shown that drugs of abuse disrupt accuracy of pigeons responding under a delayed matching-to-sample baseline (MTS). However, the exact step in the memory process that is affected by these drugs is yet to be determined. As an initial approach to this problem six pigeons were trained under a MTS baseline with delays of 0, 3 and 6 sec. Control levels of accuracy were >95%, 80-85%, and less than 80% at the 0, 3 and 6 sec delays, respectively. Pentobarbital, and phencyclidine decreased matching accuracy at delay values of 0 and 3 sec, but not at 6 sec. Diazepam decreased matching accuracy at all delay values. At scopolamine doses that markedly suppressed responding, accuracy was decreased at 0 and 6 sec, but not at 3 sec. In contrast, even at doses that markedly suppressed response rates, d-amphetamine did not decrease accuracy at any delay. Of those drugs that decreased accuracy, only pentobarbital and phencyclidine showed a significant interaction between dose and delay value ($P<0.05$), but neither pentobarbital nor phencyclidine produced any significant effects compared to saline at the longest delay value, 6 sec. Taken together, the lack of dose-delay interactions, and the significant effect at the 0 sec delay, the results of this experiment suggest that if these drugs affect working memory, it may be in addition to other effects such as discriminability of, or attentiveness to, the stimuli.

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THE EFFECTS OF DRUGS ON WORKING MEMORY IN RATS: SPATIAL ALTERNATION VS. MATCHING-TO-POSITION.

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The use of delayed spatial alternation (SA) to assess working memory in rats is frequently complicated by the development of rehearsal behavior. Such behavior is minimized under a matching-to-position (MTP) baseline requiring responses at a different spatial location during the delay. The relative sensitivity of each baseline was assessed in six rats responding under a single-response SA baseline with a 10 sec delay and in six rats responding under a MTP baseline requiring five responses on the sample lever, responding on a lever mounted on the opposite wall during the delay, and delay values of 3, 10 and 30 sec. Choice response levers were retracted during the delay period in both procedures. Control performance under the SA baseline was characterized by low variability and > 90% accuracy. MTP baseline saline control % accuracy was > 95% at 3 sec, > 90% at 10 sec and > 75% at 30 sec. Under the SA baseline, larger decreases on accuracy were observed and lower doses of pentobarbital, diazepam, phencyclidine, *d*-amphetamine and scopolamine were required to produce significant ($P<0.05$) effects in accuracy compared to the effects observed in rats responding under the MTP baseline at the 10 sec delay. These results suggest that SA may be a more sensitive baseline for determining drug effects on working memory in the rat. ACKNOWLEDGMENTS: Supported by NIDA grant DA05815.

GENDER COMPARISONS OF ALCOHOL CONSUMPTION IN CYNOMOLGUS MONKEYS

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The effects of gender, menstrual cycle phase, and social setting on alcohol drinking were examined in four female and two male cynomolgus monkeys *(Macaca fuscicularis)* trained to operate a panel for access to the drinking spout. Each cage contains a panel with two retractable drinking spouts, stimulus lights, a pellet dispenser, and a horizontally-positioned dowel. Access to the drinking spout necessitated pulling and holding onto the dowel. In Experiment 1 a Fixed-Time (FT) schedule of pellet delivery was initiated to induce drinking a fruit punch flavored vehicle (0.5% Crystal Light). The drinking behavior of male monkeys was under greater and faster control by the schedule-induction procedure, suggesting an increased susceptibility to environmental influences on the generation of excessive behavior (and possibly an increased risk for excessive alcohol consumption). Subsequently, ethanol was added to the vehicle and the initial inducing events continued. All monkeys were induced to drink increasing doses of ethanol (0.5, 1.0, and 1.5 g/kg) for 30 consecutive sessions each dose. Preliminary indications of the elimination rate of alcohol over the menstrual cycle and peak blood alcohol levels suggest no menstrual cycle or gender effects. Physiological measurements indicate a significant decrease in overnight heartrate following alcohol exposure but no notable changes in cortisol levels or liver functioning. Behavioral observations revealed gender differences in dose-dependent changes in aggression (e.g., cage shaking/display) and in active investigation of the environment. In Experiment 2 (currently underway) orally self-administered ethanol is available for 16-hr sessions in these same monkeys. The FT schedule has been discontinued; however, the reinforcing properties of ethanol alone are expected to maintain consumption during these sessions.

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EVALUATION OF A DRUG RECOGNITION SCREENING EXAM

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The Drug Recognition Test (DRT) was originally developed by the Los Angeles Police Department to identify drug intoxicated drivers. This test consists of an interview to assess speech, alertness and mood, and a non-invasive exam to evaluate pupil size and reaction to light, nystagmus, pulse, and presence of active injection sites. The DRT previously demonstrated a high accuracy rate and dose related sensitivity in laboratory testing (Bigelow *et. al.* 1986). We tested the sensitivity and specificity of a modified DRT (called the Drug Recognition Screening Exam-DRSE) using urine EMIT results as the gold standard. Subjects were 80 volunteers enrolled in the University of Maryland Drug Treatment Center. They were each given $10 for completing the study. One of three certified DRT examiners administered the test. Subjects' urine was analyzed by EMIT for marijuana, opioids, cocaine, pcp, amphetamines, barbiturates and benzodiazepines. Alcohol was also tested for in the urine. Positive drug tests were confirmed by GC/MS. Thirty-one DRSE's correctly identified the presence of any drug or alcohol in the urine. The sensitivity of the DRSE was 0.72, while its specificity was 0.70. Cohen's Kappa was 0.4. There was no pattern by specific drug type for the 12 false negative screens. The DRSE's performed in this outpatient study were not as sensitive as in the laboratory study (Bigelow 1986). This was expected since the DRSE is a test of drug intoxication, while urine EMIT can be positive even days after the intoxicating effects have cleared. The DRSE is a promising screening test for drug intoxication in an outpatient setting. Future studies should determine which elements of the DRSE are most critical in correctly identifying recent drug use.

Bigelow, G. E.; Bickel, W. K.; Roache, J. D.; Liebson, I. A.; Nowowieski, P. Identifying Types of Drug Intoxication. In: Harris, L. S., ed. Problems of Drug Dependence 1985. Wash., D.C.: DHHS Pub. No. 86-1448, 1986, p. 492.

DETERMINATION OF DRUG EXPOSURE USING HAIR: APPLICATION TO CHILD PROTECTIVE CASES

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The use of hair as a specimen for the determination of drug use remains controversial. Scientists disagree upon whether environmental drug contamination (e.g. smoke) can be differentiated from actual drug use. Children whose parents use drugs (particularly crack) at home are considered to be at risk. Using the hair of the children to determine exposure gives extra credibility to the child protective services and allows them to remove children from dangerous households. Children are tested when there are credible reasons for suspecting drug exposure. In Blackhawk County, Iowa, this program was implemented in 1994, and since then many children have tested positively for drugs, the majority of the hair containing cocaine or methamphetamine. In some cases, cocaethylene and benzoylecgonine were also found in the hair of the children. While the presence of benzoylecgonine can be explained by exposure to crack smoke, the presence of cocaethylene suggests ingestion of cocaine and alcohol. Blackhawk County Juvenile Court have found the program to be so useful in helping children, that they have extended hair testing from Child Protective allegation investigations to ongoing court cases and even delinquency hearings.

MEASUREMENT OF ANABOLIC STEROIDS IN HAIR

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A sensitive, specific and reproducible method for the quantitative determination of stanozolol (ST) in hair has been developed. Deuterium labeled ST was added to 20 mg hair samples that were digested with 1 N NaOH at 65°C for 2 h. Calibration standards containing known concentrations of ST dried onto drug-free hair were also prepared and digested. After digestion, the solution was cooled and adjusted to pH 6.0 with 6 N HCI and 1 mL of 100 mM phosphate buffer. The digest solutions were extracted with a solid-phase extraction procedure. Extract residues were derivatized and analyzed on a Finnigan 4500 mass spectrometer in negative-ion chemical ionization mode with methane reagent gas, helium carrier gas and a HP-1 capillary column (15m - 0.2 mm id - 0.33 pm). The assay was capable of detecting 50 pg/mg of ST and was linear to 2500 pg/mg. Intra-assay precision was 13.2% at 50 pg/mg and 6.6% at 2500 pg/mg. Inter-assay precision was 13.7% at 50 pg/mg and 6.1% at 2500 pg/mg. This method has been used to study the hair incorporation of ST into Long-Evans rats who received 20 mg/kg i.p. daily for 3 days. The ST concentration (mean ± SD, n=5) in pigmented and nonpigmented hair was 362.4 ± 332.4 pg/mg and 90.0 ± 46.9 pg/mg, respectively. These data demonstrate that ST is incorporated into hair (preference for pigmented hair) and can be measured by mass spectrometry.

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QUANTITATION OF METHADONE, EMDP AND EDDP IN HUMAN AND RAT HAIR BY GC/MS

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A sensitive and specific method for the quantitative determination of Methadone (MD) and its major metabolites (EMDP and EDDP) in hair has been developed. Deuterated internal standards of MD, EMDP and EDDP were added to 20-mg hair samples and digested overnight in 1N NaOH. Calibration standards containing known concentrations of MD, EMDP and EDDP dried onto human hair were also prepared. After digestion, 100 µL of methanol and 1 mL of saturated sodium borate buffer were added to each specimen, vortexed, and pH adjusted to 9.0. Four grams of NaCl were then added, followed by 4 mL of butyl chloride:acetonitrile (4:1, v/v). Specimens were extracted for 1 hr, centrifuged for 10 min. and the organic phase separated and evaporated to dryness at 40°C. Extract residues were reconstituted in butyl chloride and analyzed with splitless injection on a Finnigan Magnum™ ion trap mass spectrometer.

Chromatographic separation was achieved with helium carrier gas on a DB5MS-30m-0.25µ capillary column. Positive chemical ionization was utilized with acetone as the reagent gas. The assay was linear from 0.5 ng/mg (MD and EDDP) or 1.0 ng/mg (EMDP) to 50.0 ng/mg (r>0.99). Intra-assay precision was less than 15% for all three analytes at 2.0 and 10 ng/mg (n=6 each). Recovery was estimated to be greater than 70% for MD and EDDP and 53% for EMDP at two concentrations (2.0 and 10.0 ng/mg, n=5 each). The method has been applied to analysis of MD, EDDP and EMDP in hair obtained from human subjects receiving known doses of methadone treatment in clinical trials.

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QUANTITATIVE DETERMINATION OF BUPRENORPHINE AND NORBUPRENORPHINE II HAIR BY LC/MS/MS

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A sensitive and specific method for the quantitative determination of buprenorphine (BU) and norbuprenorphine (NBU) in human hair has been developed. Deuterated internal standard (BUd4) was added to 20-mg hair samples and digested overnight at RT in 1N NaOH. Calibration standards containing known concentrations of BU and NBU dried onto human hair were also prepared. After pH adjustment, digest solutions were buffered and extracted with butyl chloride:acetonitrile (4:1, v/v), followed by evaporation to dryness at room temperature. Extract residues were reconstituted in 70:30 MEOH:H20 prior to injection on the Finnigan TSQ^{TM}7000 LC/MS/MS (APCI ionization). Chromatographic separation was achieved on an Alltech C8 Solvent Miser® column (2.1 x 150 mm) with an isocratic mobile phase of H20:MEOH:ACN (25:30:45) containing 0.1% formic acid at a flow rate of 0.75 mL/min. The assay was linear from 10 pg/mg (BU) or 25 pg/mg (NBU) to 50 ng/mg (r>0.99) for both analytes. Intra-assay precision (n=3) was 12% at 10 pg/mg (BU), and less than 10% at 100 pg/mg, 1 ng/mg, and 25 ng/mg for BU and NBU. Recovery was determined to be greater than 74% for both analytes at 100 pg/mg, 1 ng/mg and 25 ng/mg. The method is currently being used to quantitate BU and NBU in human and rat hair obtained in dose-response studies, as well as human subjects in clinical treatment programs.

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DOSE-RESPONSE CHARACTERIZATION OF SIDESTREAM CIGARETTE SMOKE: IMPLICATIONS FOR A FETUS

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A dynamic dose-response characterization of the rodent's acute physiological response to sidestream smoke (SS), a model for passive smoking, was conducted. Young adult female SD rats were anesthetized (ketamine/xylazine) and catheters (PE50) were implanted into the carotid artery. After 24 hr recovery, the rats were exposed to the SS smoke (diluted 50%, 75% or 90%) from a reference cigarette (1R4F) burned under standard FTC conditions (0.8 mg nicotine, 11.6 mg CO, 9.2 mg tar and 10.8 mg TPM). Periodic arterial samples were drawn prior, during, and for 1 hr subsequent to the 8-min cigarette smoke exposure, Transient (~5 min) peak dose-response changes in pO_2 (54, 60 & 63 mmHg), pCO_2 (47, 52 & 53 mmHg), and pH (7.15, 7.23 & 7.37) were noted for the 50%, 25%, and 10% SS-exposed females, respectively. Dose-response changes in peak COHb elevation occurred after the 8th puff (17%, 26%, and 32%, respectively), but all returned to approximate baseline conditions by 1 hr post-exposure. Although the significance of such transient changes in blood gases for a pregnant rat and her fetuses is questionable, the protracted elevation of maternal COHb may underlie the behavioral and neurological deficits previously reported in prenatal SS-exposed offspring.

ACKNOWLEDGMENTS

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AROUSAL MODULATED ATTENTION IN NEONATES IS NOT AFFECTED BY MATERNAL TOBACCO SMOKING

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Growing concerns have been raised as to the potential effects that maternal tobacco use might have on newborn behavior. Indeed, the effects of intra-uterine cocaine exposure (CE) have been argued to be due to tobacco exposure (TE) since CE is largely confounded by TE among cocaine-using pregnant women. Since we have shown strong effects due to CE on arousal modulated attention (AMAtt: CE infants fail to show AMAtt, preferring greater stimulation regardless of arousal), we asked what effects could be attributed to TE on AMAtt? Healthy infants (n=104) from the term nursery who were not CE were identified, 32 of whom with mothers who reported smoking at least 1-2 packs/day during pregnancy. Infants' visual temporal frequency looking preferences as a function of arousal condition (feeding and additional stimulation) were evaluated. No significant main effects or interactions with TE were obtained despite sufficient statistical power to detect them. Indeed, any marginally significant direction of TE-related changes were more consistent with effects shown for CNS-injured infants tested from our laboratory who seek less stimulation with higher arousal and not with effects shown for CE infants who seek more stimulation with higher arousal. Similar effects were obtained if analyses were restricted to smokers who reported two or more packs/day usage. Testing at one month (n=87; 28% smokers) replicated neonatal effects. ACKNOWLEDGMENTS: Supported by NIDA grants R-01-DA-O6644 and K-21-DA-00236, and NICHD grant R-01-HD-21784.

PSYCHOLOGICAL AND ASI OUTCOMES FOR 3 SUB-GROUPS OF DRUG ABUSING WOMEN

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Change scores are often used to demonstrate treatment response. Unfortunately, this methodology can obscure findings for homogeneous sub-groups. Accordingly, we clustered pre-treatment MCMI-II scores of 63 drug abusing women, deriving 3 sub-groups which were compared at Intake and following completion of a 20-week long treatment program. Outcome measures consisted of three sets of MCMI-II scores (Validity, Axis I, and Axis II scales) and the ASI. At Intake, between-groups differences were found for the MCMI-II (all MANOVA $p < .0001$) and the ASI (MANOVA $p = .0269$). The only demographic variable which distinguished between groups was familial addiction, those in Cluster 1 evidencing higher rates. The groups remained distinct at follow-up on the MCMI-II (MANOVA $p = .0002$; .0165; and $< .0001$); however, their ASI scores converged (MANOVA $p = .1183$). Response to treatment varied by cluster. Cluster 1 showed no improvement on either outcome measure, retaining MCMI-II high points on ASP and Drug Dependence. Cluster 2 generated an essentially normal profile (only highpoint on Drug Dependence). Although Cluster 3 improved statistically, they retained highpoints on 8/13 Axis II scales and Drug Dependence. ASI scores for Clusters 2 and 3 improved and were not distinguishable from those of Cluster 1. Findings suggest that pre-treatment personality subgroups should be considered when assessing response to treatment. Our Cluster 1 subjects, who presented a "classical" picture of addiction (with a likely genetic component) in combination with ASP, were not helped by intensive, psychiatrically- oriented treatment; whether they would have benefited from a different program is an empirical question. Cluster 2 subjects were symptomatic at Intake, but reconstituted with treatment. The fact that the most disturbed patients (Cluster 3) improved on the ASI yet continued to evidence significant psychopathology on the MCMI-II suggests that multiple measures should be employed when assessing outcome.

PRENATAL COCAINE ALTERS PROGENY NEUROENDOCRINE RESPONSES TO SUBSEQUENT COCAINE CHALLENGE

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We have previously reported that prenatal exposure to cocaine can alter the serotonergic regulation of plasma hormones in progeny via directly acting 5-HT agonists and indirectly acting 5-HT releasers. Since plasma hormone responses to cocaine involve a serotonergic component, we hypothesized that the neuroendocrine responses to acute postnatal cocaine challenge would also be altered in progeny exposed prenatally to cocaine. Pregnant Sprague-Dawley rats (8-10/group) were administered 0.9% saline (1 ml/kg) or 15 mg/kg (-)cocaine (s.c., b.i.d.) from gestational day 13 through 20. Male and female progeny (7-10/group) were tested at a prepubescent age (postnatal day 28;PD28) while female progeny were also investigated as adults (PD45). Functional alterations were determined by measuring changes in plasma hormone responses to a single subcutaneous injection of 15 mg/kg (-) cocaine. In premibescent male progeny, the ACTH response to postnatal challenge with cocaine was potentiated by prenatal cocaine exposure whereas, in female progeny, ACTH was elevated to a comparable extent in both prenatal groups. Prenatal cocaine exposure did not alter the inhibition of renin by cocaine in male progeny but it reduced basal renin and the inhibition of renin by cocaine in female progeny. Oxytocin was not significantly elevated above basal values by acute cocaine challenge at this developmental age. In adult female progeny, the cocaine-induced elevation of ACTH and oxytocin was eliminated by prenatal exposure to cocaine. Likewise, prenatal cocaine exposure decreased basal renin levels and abolished any further inhibition of renin by cocaine. These data indicate: (1) neuroendocrine responses to cocaine can be altered by prior *in utero* exposure to this drug, and (2) the alterations produced may be influenced by gender and postnatal age.

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THE EFFECTS OF PRENATAL COCAINE ON INTRAVENOUS COCAINE SELF ADMINISTRATION

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Although the effects of prenatal cocaine on subsequent cocaine responsivity have been well examined, there are little data on how such exposure affects the subsequent vulnerability to the reinforcing properties of cocaine. Recently, Keller and his colleagues (Neurosci. Letters. 205:153-156; 1996) demonstrated that animal prenatally exposed to cocaine responded at a higher level for a 0.40 mg/kg dose of cocaine than pair-fed control subjects. As noted by Keller *et al.* (1996), however, conclusions based on differences at a single dose must be cautiously made given that one does not know where on the dose-response function this specific dose may lie and if the response functions differ for animals with different prenatal histories. To address this issue, in the present experiment animals prenatally exposed to cocaine were subsequently trained to self-administer cocaine across a wide range of doses, allowing an assessment of a dose-response function for cocaine self-administration. These subjects were compared to subjects exposed to the cocaine vehicle as well as subjects exposed to cocaine prenatally and perinatally. Although the peak number of infusions did not vary among the three groups, both cocaine-treated groups displayed peak responding at lower doses of cocaine than the control group. Further, the smallest dose that supported cocaine self administration was lower for the cocaine-treated groups with the group receiving cocaine during gestation and following delivery self administering cocaine at the lowest dose. The present data are consistent with other reports demonstrating changes in behavioral vulnerability following cocaine pre-exposure and suggests that animals with these histories are more sensitive to the reinforcing effects of cocaine. ACKNOWLEDGMENTS: Research supported by NIDA grant 1 F31 DA05641-01

NEUROBEHAVIOR AS A FUNCTION OF IN UTERO COCAINE EXPOSURE AND PRENATAL CARE IN TERM NEONATES

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Inconsistent results have been reported for neonatal neurobehavioral evaluations in cocaine-exposed (CE) infants. Some of these inconsistencies may be explained by the amount of stress *in utero* that can be estimated by whether the infant had adequate prenatal care (PC) and by the occurrence of medical problems that can be estimated by whether the infant was assigned to the term nursery or NICU. In the present study, infants from the normal term nursery were classified into four groups using a 2x2 design: CE+no-PC (n=64); CE+PC (n=29); no-CE+no-PC (n=46); and no-CE+PC (n=89). We found an additive effect of CE and PC on hypertonicity of the upper extremities and on jitteriness, with the proportion of abnormalities detected across the four groups = .60, .52, .54, and .22 for hypertonicity and .41, .34, .33 and .08 for jitteriness. Lower extremity hypertonicity was related more to PC than to CE. Visual asymmetry was related to PC, while visual attention was related to CE. There also was some increase in peak excitement (irritability) as a function of CE. This is interesting since we find arousal modulated attention effects related to CE not PC during this period. These neuro-behavioral motor effects appear to be transient whereas the sensory/ perceptual ones may not be, as we do not find motor deficits on the Bayley Scales at older ages but do find mental score decline after a year.

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COGNITIVE DEVELOPMENT IN PRENATALLY SUBSTANCE-EXPOSED CHILDREN: CROSS-SECTIONAL AND PROSPECTIVE DATA

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Studies have found approximately 11 % to 19% of newborns in the United States have been prenatally exposed to drugs and/or alcohol. These children are at high risk for developmental delays and behavioral problems and caregivers often report significant stress. For the past three years, the Child Study Center at the OU Health Sciences Center has conducted a longitudinal study of prenatally substance-exposed children and their families. The children were administered the Bayley Scales of Infant Development-II, and the parents/caregivers completed the Parenting Stress Index (PSI) and the Achenbach Child Behavior Checklist (CBCL). Cross-sectional analyses (N = 85; 37 males, 48 females) demonstrated a significant decrease in cognitive functioning between 12 and 24 months of age ($p < .001$), as well as an increase in parent-child relationship stress ($p < .02$). Prospective examination of a sample of 25 children (13 males, 12 females) at both 12 and 24 months of age was also completed. Although cognitive functioning at 12 months of age was within normal limits, significant developmental delays were evident at 24 months ($p < .01$). This finding appears to be independent of placement and type of prenatal substance exposure, supporting cross-sectional findings. Although child-related stress tended to increase over time ($p < .08$), other aspects of parenting stress did not change, contrary to the results of cross-sectional data. In addition, the level of parent-reported behavioral problems on the CBCL were inversely correlated with cognitive functioning at 24 months. These findings, though preliminary in nature, suggest that prenatal substance exposure may adversely affect children's cognitive functioning over time and increase child-related parenting stress. However, intervention with the prospective sample appears to improve some aspects of the family relationship.

PRENATAL SUBSTANCE EXPOSURE AND CHILD IQ: THE ROLE PLAYED BY VARIOUS RISK FACTORS

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Whether a relationship exists between prenatal substance exposure and mental development is unclear; it is likely that other risk factors also affect child outcome. This study hypothesized that prenatal substance exposure, maternal education, parenting stress, child abuse potential, and home environment would predict child IQ. Subjects were 31 infants and their mothers who had participated in a substance abuse treatment and research program. Most of these infants (71%) were born to substance-using mothers, 73% of whom had participated a treatment program during pregnancy or the postpartum period. Most substance users were polydrug users (91%) with cocaine most often the primary substance of abuse (59%). The children's ages ranged from 29 to 61 months. Assessments coincided with either their annual or semiannual birthday. Mothers completed the Home Screening Questionnaire (HSQ), Parenting Stress Index (PSI), Child Abuse Potential Inventory (CAP), and a demographic questionnaire. Children were assessed with the Stanford-Binet Intelligence Scale. Univariate analyses revealed a significant difference in child IQ by maternal educational level (p = .03), and trends for significant differences in IQ by substance exposure status (p =.07) and home environment quality (p = .09); relationships between child IQ and both PSI and CAP scores were nonsignificant, although the direction of the relationship was in the expected direction. Using mixed stepwise multiple regression, low maternal education significantly predicted lower child IQ (p = .01); home environment demonstrated a trend toward predicting lower child IQ (p =.09).

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NEONATAL, PHYSICAL AND BEHAVIORAL OUTCOMES IN SELF REPORTED SUBSTANCE ABUSING MOTHERS WITH NO PRENATAL CARE

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The impact of both licit and illicit prenatal substance use on pregnancy outcomes is of increasing societal concern. Lack of prenatal care also has been found to contribute to pregnancy outcomes. Data presented are from a subset of pregnant African American subjects who had no prenatal care (N=140) and those who had care (N=361) who delivered infants at Howard University of D.C. General Hospitals, Blood samples and information regarding the use of illicit drugs (PCP, marijuana and cocaine) were collected from each subject. Data on infant birth weight, birth length, head circumference and gestational age we obtained at birth. In addition, Brazelton neonatal behavioral assessments were performed within two days after birth. Overall, infants of mothers who received no prenatal care had significantly lower (P=0.000) gestational age, head circumference, body length, birth weight than infants of mothers who received prenatal care. In addition, they performed significantly lower (P0<.002) on BNBAS motor and BNBAS Habitation clusters. Among the subjects who received no prenatal care, self reported drug use showed an incidence of 35% which is three times the estimate of the National Pregnancy and Health Survey (NIH). Self reported drug users had significantly (P0<.05) lower birth weight (2336.0±124.18) compared to those who did not use drugs (2835.5±110.5g). For subjects receiving prenatal care infants of drug users had significantly lower (P0<.05) head circumference and shorter body lengths. Results bear implications for the interaction of prenatal care and drug use on outcomes.

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NUTRITIONAL INTERVENTION IN THE TREATMENT OF COCAINE-DEPENDENT PREGNANT WOMEN

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The purpose of this ongoing study is to assess the nutritional status of cocaine-dependent pregnant women who are participating in a comprehensive treatment program designed to decrease cocaine use and increase compliance with the treatment regimen. Subjects are pregnant women who are 28 weeks of gestation or less, with a primary diagnosis of cocaine dependence, or opiate dependence with secondary cocaine dependence. They are randomly assigned to one of three treatment groups. Patients in all three groups receive baseline treatment which includes: behaviorally-based individual counseling twice a week, group therapy/parenting skills class, HIV pre- and post-test counseling and testing, and prenatal care once a week. Patients are required to attend the Substance Abuse Prenatal Clinic once a week and the Treatment Research Clinic (TRC) twice a week, providing a urine sample at each of these visits. All subjects are also required to complete a nutrition questionnaire which includes a 24-hour dietary recall and a food frequency at the beginning and end of the study. A nutritional analyses of this data is performed using a Nutritionist IV software program. Blood analyses including assessment of serum albumin, total protein, hematocrit and hemoglobin is also conducted. Preliminary results indicate that a significant number of patients (higher than 25 percent) have less than acceptable levels of serum albumin, hematocrit and hemoglobin. Analysis of the dietary data reveals deficiencies of several essential nutrients. This preliminary data has significant implications as it has been indicated that maternal nutrition can influence reproductive performance, especially of women (such as in this study), who have a high risk of giving birth to low birth weight infants.

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NUTRIENTS AND BIOCHEMICAL VARIABLES IN SELF-REPORTED SUBSTANCE ABUSING MOTHERS WITH NO PRENATAL CARE

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The development of the fetus is usually compromised by the nutritional status of substance abusing mothers. We previously reported that serum concentrations of folate and ferritin were significantly lower in pregnant women with serum illicit drug levels above the ADAMHA/NIDA ranges. The data reported are from a subset of 140 subjects who received no prenatal care (NPC) and were enrolled in a nutrition program project. Information illicit drug use (PCP, marijuana, cocaine and methamphetamine) was obtained from an entry questionnaire. Self reported drug use showed an incidence of 34% with no responses from 24% of the subjects. Nutrients and biochemical variables were similar among subjects who reported “yes” or “no” to drug use during pregnancy of $P>0.05$. Drug use among participants before pregnancy, resulted in a significant decrease in total protein (13% less; $P=0.013$) and globulin (35% less; $P=0.006$) when compared to no reported usage. Subjects who received NPC had serum folate and vitamin B_{12} levels 62% and 26% respectively less than those who received prenatal care.

CONTRIBUTION OF SUBSTANCE ABUSE TO INFANT MORTALITY IN AN INNER CITY POPULATION

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This report analyzes the first 66 infant deaths which occurred in 1994 and reviewed as part of the Fetal and Infant Mortality Review for the District of Columbia Healthy Start Project. Data on the remaining 12 deaths and 78 controls is currently being prepared for analysis. Maternal profile shows that the ages of women were: <17 years old, 8%; 17-24 years, 32%; 25-34 years, 51%; and >34 years, 9%. Also, 98% were black and 2% were white; only 15% were currently married; 47% had less than a high school education, 43% had a high school education, and 10% had some college education: and 74% were unemployed. Prevalence of substance abuse during pregnancy was as follows: crack cocaine, 24%; alcohol, 33%; cigarette smoking, 50%. These women tended to lack social support: 38% did not get a visit from the infant's father, 68% did not list husband or boyfriend as next of kin, 59% dropped in without prior arrangement, and 73% were transported to the delivery hospital by EMS team. Substance abuse contributed to infant deaths mainly through pre-term labor and premature delivery: <750 grams, 60%; 750-1499 g, 11%; 1500-2499 g, 12%; <28 weeks, 67%; 28-31 weeks, 5%; 32-36 weeks, 11%.

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PSYCHOLOGICAL STATUS AND PARENTING BEHAVIORS IN COCAINE-USING MOTHERS

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This study was based on the hypothesis that differing psychological profiles in substance-abusing mothers of child-bearing age may be associated with varying levels of sensitive parenting. Subjects were 151 cocaine-using pregnant women enrolled in a research demonstration project examining the effectiveness of substance abuse treatment in promoting abstinence and improved parenting behaviors. All subjects completed the Millon Clinical Multiaxial Inventory II (MCMI) and Addiction Severity Index (ASI) at intake (average 29 weeks gestational age), and mother-child interaction was observed in the home using a maternal behavior rating scale one and six months post delivery for 83 subjects. Cluster analysis of MCMI scores suggested the presence of three clusters: a low-risk cluster (N=58) of women whose profiles fit the MCMI pattern of drug dependence (mean=77) and associated antisocial characteristics (mean=79); a moderate-risk cluster (N=29) characterized by multiple elevated MCMI scale scores (mean>75), including dysthymia (mean=90); and a high-risk cluster (N=64) with elevated MCMI scale scores (mean>75), including delusional (mean=84) and thought disordered (mean=75) symptomatology. The clusters did not differ on the ASI drug abuse composite at intake or on parenting behaviors at one month post delivery. Irrespective of treatment or comparison group status, subjects (N=83) showed the following trend: On the ASI drug risk composite, intake to six months post delivery, the most high-risk cluster demonstrated the greatest change, but this was not statistically significant. Also, women in the low-risk MCMI cluster showed significantly more sensitive parenting six months post delivery than those in the other two clusters. Thus, there may not be a strong association between decreased drug use by self-report and better parenting. Parenting behaviors in this group of substance-abusing mothers were dependent on another factor--maternal psychological status.

PSYCHOLOGICAL FACTORS AFFECTING PARENTING AMONG SUBSTANCE ABUSING WOMEN

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The impact of drug dependence on psychosocial functioning has been well documented. Little is known, however, about the relationship between drug dependence, psychosocial functioning and parenting knowledge. The present study examined the demographic and psychosocial factors that may be correlated with parenting knowledge and attitudes in pregnant drug dependent women attending a comprehensive substance abuse treatment program in Baltimore, Maryland. We study this in a sample of 197 substance abusing women (mean [SD] age 28.59 [4.7], mean years of education 11.03 [1.56] amd 85.7% African American). All subjects completed the Addiction Severity Index within three days post-admission and a Parenting Skills Questionnaire (PSQ) within seven days post-admission. The PSQ consists of 29 true-false items which assess four parenting domains: newborn care, feeding, child development, and drug abuse and pregnancy. Correlations coefficients and T-tests were used to compare 37 ASI variables with four domain and total PSQ scores. There were few significant ASI psychosocial variables correlated with PSQ scores (ourt of 185 correlations, only 15 [8.1%] were significant). Current living situation items (living with a partner or not, living with someone with an alcohol and/or drug problem) were the ASI factors that appeared to be most related to the PSQ scores. The results suggest that the PSQ has external consistency because the test scores appeared not to be greatly affected by psychosocial factors.

CRACK USE AND FERTILITY PATTERNS AMONG WOMEN ARRESTED IN MANHATTAN

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Women who use crack have different fertility patterns than women with other patterns of drug use. This is a secondary analysis of the Drug Use Forecasting Program (DUF) data. DUF interviews arrested women booked for felony and misdemeanor crimes, regarding demographics, arrest charge and self-reported drug use. A DUF-Manhattan supplement obtains information about: types of heterosexual partners, sexual self-identities, and their pregnancy histories since 1990, whether various drugs were used during pregnancies, and self-reported pregnancy status at the time of interview. Urine specimens are collected from DUF participants and tested for ten drugs and for pregnancy. Women are classified according to the most serious drug(s) used and the number of days in the past 30 the specific drug(s) were used. DUF-Manhattan women have very high levels of cocaine and crack use, both self-reported and detected. Two-thirds have been arrested on felony charges and most engage in some form of high-risk drug or sexual behavior. Crack-using women are hypothesized to have a younger age at first pregnancy, but they may have fewer children than other women. They may also differ in the number of reported abortions and miscarriages. Crack users are more likely to exchange sex for drugs or money and to identify themselves as prostitutes. Results will be important for drug treatment programs both within and outside of the criminal justice system. Likewise, foster care and other child-service agencies, public health agencies and educational institutions will find results useful as they relate to crack-using women and their children.

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PREVENTION OF RELAPSE TO COCAINE USE DURING PREGNANCY

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There are data to indicate spontaneous cessation of cocaine use among cocaine-dependent women during pregnancy. As with other cocaine dependent patients in treatment, risk of drug relapse may be present. The **purpose** of this study is to determine the effectiveness of contingency management, as an adjunct to a behaviorally-based baseline treatment, in preventing relapse and maintaining compliance with prenatal care, in pregnant cocaine-dependent women who had ceased cocaine use prior to entering treatment. **Methods:** Pregnant women with a primary diagnosis of cocaine dependence, who reported no cocaine use one month prior to treatment entry and who were cocaine-free at intake, were randomly assigned to were assigned to one of two groups. Patients received baseline treatment: behaviorally based counseling, prenatal care, HIV pre and post-test counseling and testing, and transportation and child care. Patients were required to attend clinic three times per week, and provide a UA at each visit. In addition to baseline treatment, patients in Group A were reinforced ($18) for each cocaine-freeUA, with additional weekly reinforcer ($20) if they attended clinic all three days and all three UAs per week were cocaine-free. Patients in Group B received baseline treatment alone (Control group). **Results:** Data are reported on 12 patients, six per group. (a) Treatment retention: 91% completed treatment, with no significant differences between groups. (b) Cocaine UAS: 91% UAs were cocaine-free. Group A had a significantly higher rate of consecutive cocaine abstinence (94%) than Group B (69%) [p=0.05] (c) Prenatal compliance: Group A had higher rates of prenatal compliance with clinic visits (100%) than Group B (83%) [p=0.07]. (d) Perinatal Risk Factors: Four perinatal risk factors associated with cocaine use and poor prenatal care were examined. Significantly more patients in Group A (100%) had none of these risk factors compared with Group B (20%) [p=0.01]. **Conclusions:** Pregnant women who cease cocaine use prior to treatment entry have extremely high rates of treatment retention, cocaine abstinence and 'prenatal compliance. Contingency Management Interventions improve consecutive cocaine abstinence, prenatal compliance and is associated with improved perinatal outcome. Acknowledgements: Supported by a grant from the NIDA (DA-08438)

PSYCHOSOCIAL FACTORS ASSOCIATED WITH PREMATURE TREATMENT DROPOUT IN PREGNANT SUBSTANCE ABUSERS

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Length of stay is one of the primary variables affecting drug abuse treatment effectiveness. While opiate-dependent individuals in methadone maintenance have relatively high retention rates, opiate-dependent individuals in abstinence-based treatment are more likely to drop out prematurely. The present study examined the effect of two treatment strategies for treating opiate withdrawal on treatment retention. Patients were 112 pregnant opiate-abusing women admitted to treatment between 1/95 and 2/96. Patients were classified as taper (N=56) if they were prescribed a three-day methadone taper for opiate withdrawal management or non-taper (N=56) if they received alternative, non-narcotic withdrawal management treatment. There were no demographic differences between the two groups. Despite similar substance use histories, taper patients were 1.4 times more likely to leave residential treatment against medical advice (AMA) than non-taper patients ($p<.04$). For patients transferring to outpatient care, non-taper patients remained in treatment eight times longer than taper patients ($p<.003$). Additional research is needed to further assess the clinical utility of a three-day methadone taper for withdrawal management in opiate-abusing pregnant women.

A PROFILE OF PREGNANT DRUG-USING ARRESTEES IN CALIFORNIA

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Data from 140 pregnant drug-using females from a sample of 1,557 female arrestees who participated in the CAL-DUF Program in 1993 and 1994 were analyzed. The profile indicated that: (a) they were young (mean age = 28.1 years), (b) they were overrepresented by black women (38%), (c) they were predominantly single (42%), (d) a majority were on public assistance (82%) (e) their charges were related to nonviolent crimes and drug use, and (f) 51% had not completed high school. Seventy-eight percent tested positive for a single drug and 22% tested positive for two or more drugs. The mean addiction career was nine years. Only 21% had previously received substance abuse treatment and 28% stated that they currently needed treatment. Younger women (< 28 years) were more likely to have initiated use of powder and crack cocaine, methamphetamine, and tobacco and to have injected drugs earlier than older women. Black women were more likely to test positive for cocaine and white women were more likely to test positive for methamphetamine and to have injected drugs or shared needles. Logistic regression analysis identified a previous miscarriage and a high school diploma or GED as significant predictors of prenatal care utilization. A significant predictor of prior substance abuse treatment was current perceived need for treatment.

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ACHIEVING ABSTINENCE IN PERINATAL COCAINE-DEPENDENT WOMEN: A CONTINGENCY MANAGEMENT APPROACH

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Cocaine dependence among pregnant women and mothers of young children is a major public health problem. Contingency management involving voucher-based incentives for abstinence has shown efficacy in other groups of cocaine abusers. In this study, we adapted and tested this treatment in a sample of 24 pregnant and post-partum inner city women. The contingency management intervention lasted 12 weeks and involved three times weekly urine testing and rewards for abstinence in the form of vouchers exchangeable for goods and services. It was hypothesized that subjects receiving enhanced treatment, *i.e.* contingency management plus treatment as usual in their partial day treatment program, would achieve longer retention and higher rates of abstinence than historical controls from the same clinic who had received standard treatment only. Subjects in the experimental (enhanced treatment/ voucher) group attained significantly higher rates of abstinence (57% cocaine-free urines vs. 27% in the control group, $t=-3.5$, $p<.001$) and longer periods of continuous abstinence while in treatment (4.2 weeks vs. 1.3 weeks in the historical control group ($t= -2.9$, $p<.008$). In the experimental group, 45.8% of subjects attained rates of abstinence of 80-100% during treatment, vs. 4.1% of the historical control group; and fifty percent of the historical control group had less than 20% cocaine-free urines while in treatment compared to 20.8% in the experimental (voucher) group. There were no significant differences found between the two groups in length of retention in treatment.

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PREVENTION OF RELAPSE TO COCAINE USE IN POST-PARTUM COCAINE-DEPENDENT WOMEN: CONTINGENCY MANAGEMENT INTERVENTIONS AND COGNITIVE-BEHAVIORAL THERAPY COMPARED TO SUPPORTIVE COUNSELING

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Cessation of cocaine use during pregnancy has been viewed as a window of opportunity for change. However, there is a risk of relapse to drug use following the birth of the baby. The **purpose** of this study is to compare two treatment methods in preventing relapse to cocaine use in post-partum women who had completed an outpatient treatment program for drug-dependent pregnant women and were either cocaine-free throughout or had high rates of cocaine abstinence during treatment participation. **Methods:** Upon completion of the pregnancy project, patients who had at least 33% cocaine-free UAs during study were eligible to enter the post-partum study (12 weeks). Patients were randomly assigned to one of two treatment conditions, with two clinic visits per week. Patients in **Group A** received cognitive-behavioral treatment which consisted of coping skills training. In addition, they received reinforcement for each successive decrease in cocaine metabolite levels ($10). Patients also received a larger magnitude reinforcer ($12) for each cocaine-free UA, and an additional weekly reinforcer ($15) if they attended clinic on both days and both of the urine samples per week demonstrated a decrease in cocaine use of were cocaine-use or were cocaine-free. Patients in Group B received supportive therapy only. **Results:** Data presented on 20 patients. (a) Treatment retention: 77% completed study, with no significant differences between groups. (b) Cocaine-abstinence: (i) There was an increase in cocaine use post-partum (25%) compared to during pregnancy [p=.013]. (ii) Proportion of cocaine use during pregnancy predicted cocaine use post-partum [p=0.002]. (iii) There were no significant differences between the two treatment groups in cocaine use post-partum. **Conclusions:** High rate of retention in treatment. High rate of abstinence from cocaine post-partum. although higher rates of cocaine use post-partum compared to pregnancy. Proportion of cocaine use during pregnancy predicted use post-partum. Rates of abstinence during post-partum treatment not significantly different between groups. Type II error may exist. Results applicable only to patients with significant levels of abstinence from cocaine during pregnancy. Acknowledgements: Supported by a grant from the NHIA (DA-08438)

ATTITUDES AND BELIEFS OF NURSES AND PHYSICIANS WHO CARE FOR PREGNANT SUBSTANCE-ABUSING WOMEN

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Background: Women with a history of drug use who become pregnant are often subject to biased attitudes throughout the health care system. Providers' attitudes toward these women influence compliance, possibly affecting prenatal care, and subsequent pediatric care. Non-judgmental, supportive care strategies may be of significance in improving compliance with care provided during pregnancy, delivery, and beyond. Examination of attitudes and beliefs of health care providers who care for pregnant women with a history of drug use is essential to initiating interventions which best address the comprehensive health care needs of this population. **Purpose:** To describe the attitudes of health care workers (nurses and obstetricians) toward substance abusing pregnant women. **Methods:** 1500 survey forms were distributed to a sample of obstetrical nurses (RN's and LVN's) and obstetricians throughout the State of Texas. **Results:** Data reported on 73 MDs and 176 Rns (9.7% and 23.5% response rate). (a) Experience: Both MDs and RNs had treated patients with a history of drug use. (b) Teratogenic Effects on Fetus: Cocaine was reported as most harmful drug by both MDs and RNs, followed by heroin and alcohol. RNs reported heroin to be more harmful than MDS (p=0.002). MDs reported alcohol to be more harmful than RNs (p=0.001. RNs reported cigarettes to be more harmful than MDs. (c) Treatment Planning: Most MDs and RNs reported conducting UAs on women who reported use and not on those who did not report. (d) Interventions at Delivery: Over 50% of RNs and MDs felt that either Child Protective Services or OB Social Services should be notified at delivery of women with a history of drug use. **Conclusions:** (1) RNs and MDs have a lot of experience caring for pregnant women with a history of substance abuse. (2) Inaccurate knowledge of teratogenic effects particularly regarding cigarettes. (3) Drug use may be overlooked in women who do not report use. Acknowledgements: Supported by a grant from the NIDA (DA-08438)

PHYSICAL AND SEXUAL ABUSE IN DRUG-DEPENDENT PREGNANT WOMEN

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Rates of battering in women have been found to vary widely. A co-existence between battering and the use of alcohol/drugs by the victim or perpetrator has been reported. There has been little research done on drug-dependent pregnant women with histories of abuse or current abusive relationships. The **purpose** of this ongoing study is to determine, among cocaine-dependent pregnant women, 1) prevalence of physical/sexual abuse and 2) subjects' knowledge of available resources for battered women. **Methods:** Subjects were pregnant women dependent on cocaine, who participated in a treatment program designed to decrease cocaine use and increase prenatal compliance (N=26). **Instruments:** The Abuse Assessment Form was developed for this study to obtain physical/sexual abuse histories, as well as to assess knowledge of resources for women in abusive situations. The Recent Abuse Questionnaire is administered during treatment to monitor physical abuse during current pregnancy. The Addiction Severity Index was used to further profile the patients. **Results:** (i) Lifetime abuse: 92% reported having been physically abused by someone important to them and 1/2 of these reported receiving medical treatment for their injuries. 76% reported sexual abuse at some time in their lives. Mean age of first incident was 15 years (range: l - 32 years). Mean age of first incident of sexual abuse for Caucasians was five years and for African-Americans 17 [p=0.01]. (ii) Recent abuse; In past year, 62% had been physically abused and 15% sexually abused. (iii) Abuse during pregnancy: One half of patients had been physically abused during current pregnancy (69% of these by a boyfriend/husband). Mean rate of abuse during current pregnancy was 2.7 (range 1-7). The most common area of injury was the face, and next most common the back. 12% reported current fear of abuser. (iv) Knowledge of resources: 58% of the sample were knowledgeable of community resources for battered women. **Conclusions:** Preliminary data indicate that this population has a very high rate of physical and sexual abuse, both past and current. Because of the significant risk that abuse during pregnancy poses, this data has relevance for designing appropriate treatment interventions for this high-risk population. Acknowledgements: Supported by a grant from the NIDA (DA08438)

CLONIDINE ABUSE: PREVALENCE IN A POPULATION OF SUBSTANCE ABUSING PREGNANT WOMEN.

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Clonidine hydrochloride, an antihypertensive, has been used therapeuticaly for opiate withdrawal. Recent clinical data, however, suggest the drug may have abuse potential, particularly in opiate dependent individuals. The present study examined prevalence of clonidine use in a sample of pregnant opiate abusing women. Consecutive admissions to the program reporting recent opiate use and a negative history of hypertension were invited to participate in the study. No one refused study participation. Subjects (N =90) were predominantly unemployed, African American women in their late 20's, with less than a high school education. On average, the women sought treatment late in the second trimester. Recent clonidine use was assessed by urinalysis and self-report (supplementary items on the Addiction Severity Index). One-third of the sample was clonidine positive, with over two-thirds of cases identified by positive urinalysis alone, Logistic regression identified four measures that predicted clonidine use on admission: recent clinical anxiety, high severity family/social problems, recent cocaine use, and recent prior drug treatment. Study findings suggest that the abuse potential for clonidine warrants further study.

THE FREQUENCY AND IMPACT OF TRAUMA AMONG PREGNANT SUBSTANCE ABUSERS

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This research was conducted with 103 indigent, pregnant substance abusers who enrolled in a residential treatment program. The study had three goals: (1) to document the prevalence of exposure to violent trauma; (2) to examine the prevalence of posttraumatic stress disorder (PTSD); and (3) to assess the relation between traumatic stress symptoms and treatment outcomes. Results indicated that the sample had high rates of exposure to violent trauma, such that 74% had experienced sexual assault, 73% had experienced physical assault, and 68% had experienced indirect violent trauma. High rates of traumatic stress were found in that 62% met DSM-IV criteria for posttraumatic stress disorder. Finally, regression analyses revealed that posttraumatic stress was related to psychological functioning and program completion. Findings suggest that treatment providers need to assess for trauma histories and traumatic stress symptoms.

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PERSONALITY DISORDERS AND SUBSTANCE DEPENDENCE: ASSESSMENT IN PREGNANT WOMEN

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Assessment of comorbid drug use disorders and personality dysfunction in pregnant women has important implications for treatment, intervention, and recovery. This study examined the relationship between DSM-III-R Axis II personality disorders and clusters with various measures of drug and alcohol dependence and psychosocial functioning. Subjects were 131 pregnant women enrolled in a comprehensive drug treatment program. On admission, patients completed the ASI, SCID, and SCID-II. Subjects were classified in two ways: number of personality disorders (no PD's, 1 PD, and 2+ PD's) and DSM-III-R personality clusters (A, B, and C). Age on admission was related to the number of diagnosed personality disorders (no PD's = 29.2 yrs. vs. 1 PD = 28.7 yrs. vs. 2+ PD's = 26.9 PD's). Individuals diagnosed with one or more Axis II personality disorders exhibited higher rates of Axis I mood disorders. Pregnant women with one or more personality disorders had a higher ASI Drug Interviewer Severity Rating than women without diagnosed personality disorders, even when controlling for age effects. Thus, more severe drug dependence symptomology was detected in individuals with personality disorders. Subjects with Cluster B personality disorders reported the highest number of drug treatments in lifetime, had a greater need for alcohol abuse treatment, and the highest frequency of cigarette smoking in lifetime. Also, Cluster B women displayed the highest severity of Axis I psychiatric symptomology. Multiple Regression analysis of demographic variables, selected ASI and SCID variables, and the personality disorder grouping variable indicated that age, education, personality disorder group, and family/social severity significantly contributed to 16 percent of the variance in drug severity (ASI Interviewer Severity Rating). This research suggests that individualized and intensive therapy for personality disordered pregnant women, particularly Cluster B, may be warranted in drug treatment because of greater drug severity.

AN OPEN TRIAL OF FLUOXETINE IN DRUG-DEPENDENT DELINQUENTS WITH MAJOR DEPRESSION

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Adolescents with conduct disorder (CD) and substance use disorders (SUD) have high rates of comorbid depression, which may contribute to the severity of SUD. Fluoxetine is more effective than placebo in treating depression in adolescents generally, but little is known about the response of depressive symptoms in delinquents with SUD. In an open trial, seven male adolescents (14-17) with CD, SUD, and major depression (DSM-IV) were treated with a 20 mg daily dose of fluoxetine after at least one month of abstinence from drugs of abuse. Carroll self-ratings of depression, global ratings of depression and clinical assessment of target symptoms were obtained at baseline and after at least seven weeks of treatment (mean 13 weeks). Six of seven boys' Carroll depression ratings declined ($p<.03$, two-tailed; non-parametric Wilcoxon Signed-Rank test) with a mean decline of 33% on fluoxetine. Global self-ratings of depression improved in all seven boys ($p<.02$), two-tailed; non parametric Wilcoxon Signed-Rank test) with a mean improvement of 49%. Similarly, clinician global ratings improved in all seven boys ($p<.02$, two tailed; non parametric Wilcoxon Signed-Rank test) with a mean improvement of 44%. No serious side effects, akathesia, or switching to mania were noted during the trial. Preliminary data indicate that fluoxetine may be useful treatment for depression in substance-dependent delinquents and call for controlled trial of flouxetine in such youths.

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SOCIAL ADJUSTMENT AND SUBSTANCE USE IN PREGNANT TEENAGERS

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Compared to peers who delay childbearing, adolescent mothers are more likely to engage in substance use. However, the social and psychological correlates of substance use remain unclear in adolescent mothers. This multivariate analysis examines the relationship between substance use and social adjustment using the Youth Self-Report (YSR) (Achenbach, 1991) in a cohort of pregnant teenagers. Adolescents (n = 415) interviewed at mid-pregnancy and delivery at a prenatal clinic in Pittsburgh, PA were an average age of 16.3 (12-18) years; 69% were African-American. The prevalence of drinking in this cohort was similar to that of adolescent females in national surveys, although tobacco and marijuana use were higher. Early pregnancy alcohol use was significantly related to higher scores on the social, thought disorder, attention, aggression, and delinquency problem scales. Early pregnancy tobacco use was significantly related to higher scores on the delinquency scale. Early pregnancy marijuana and other illicit drug use were not related to any of the YSR problem scales. Later pregnancy alcohol use was significantly related to higher scores on the aggression and delinquency scales. Marijuana use was significantly associated with higher scores on thought disorder, attention, aggression, and delinquency problem scales. Later pregnancy tobacco use was significantly related to more attention problems. No substance predicted higher scores on the anxiety/depression scale. These results suggest that substance use in pregnant teenagers is associated with a variety of maladaptive social adjustments, which need to be addressed in conjunction with interventions that target prenatal substance use.

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SUBSTANCE USE/ABUSE AMONG ADOLESCENTS: PRIMARY OR SECONDARY DISORDERS?

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Analyses which examined the comparative age of onset of drug use and psychiatric disturbance for adolescents admitted to residential drug treatment programs showed involvement with drugs generally preceded psychiatric disturbance. However, a caveat is offered, based on the limitations of the current analyses. Age of onset of initial drug use (alcohol or marijuana) may have limited differentiation among groups. Future analyses will examine age when regular use began.

Thus far, the profile that emerges suggests a differentiation along a spectrum of severity, which includes earlier age of onset across several dimensions - drug use, criminal activity and psychiatric disturbance. There is less specification according to order of onset, *i.e.,* psychiatric disturbance preceding or following initiation of drug use. Adolescents who manifest problem behaviors at an earlier age may require a more intensive and longer treatment impact, to address the severity and extent of their problems.

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PERSONALITY ASSESSMENT OF ADOLESCENT SUBSTANCE ABUSE/DEPENDENCE AND CONDUCT DISORDER

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Conduct Disorder (CD) among adolescents has been associated with substance use disorders (SD), but little is known about the personality dimensions related to CD or SD. Previous research suggests that sensation- or novelty-seeking, low Conscientiousness, low Agreeableness and high Neuroticism are related to substance dependence and antisocial behavior in adults. These dimensions have not been studied extensively in adolescents with comorbid CD and SD. We hypothesized that, if personality can be reliably measured in adolescents, the personality profile patterns of these adolescents with CD and SD might be similar to patterns found in substance-abusing, antisocial adults. We examined 123 (94 male and 29 female) adolescents with comorbid CD and SD using the NEO PI-R and other structured assessments. Our results appeared similar to those in adult samples in that this population showed an expected pattern of low Conscientiousness and low Agreeableness. Although the mean Neuroticism score was not elevated, Neuroticism was related to several measures of Substance Dependence. Personality Variables were also related to Conduct Disorder. Issues regarding personality assessment with adolescents are discussed.

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HETEROGENEOUS TEMPERAMENT PROFILES AMONG EARLY ONSET MULTI-PROBLEM SUBSTANCE ABUSING YOUTH

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Hypothesis: We hypothesized that multiple-problem adolescents with severe substance abuse and conduct disorder should show C. R. Cloninger's characteristic Type-II temperament profile: high Novelty Seeking (NS), low Harm Avoidance (HA) and low Reward Dependence (RD). Subjects: Participants were family members from the Adolescent Substance Abuse project, an ongoing family study of substance abuse and comorbid psychiatric problems. The current sample includes 100 "treatment" (T) families and 100 matched control (C) families (a total sample of 851 individuals). Treatment families are ascertained through male adolescents in a milieu-type residential treatment facility for substance abuse and delinquency. Procedures: NS, HA and RD were assessed using a 54-item version of Cloninger's Tridimensional Personality Questionnaire (TPQ). Substance abuse/dependence and related psychiatric symptoms were assessed through structured diagnostic interviews and self-report questionnaires. Results: Relatively modest correlations were found between the TPQ scales and severity of substance dependence as indicated by DSM-III-R substance dependence criteria. Multivariate clustering procedures indicated that 42% of the treatment probands were best characterized by a Type-II temperament profile, but 58% showed a reverse pattern of traits characteristic of a Type-I profile. The Type-II group did show increased levels of substance use and dependence in comparison to the Type-I group, but the groups did not differ significantly in related psychiatric symptoms. Although alcohol and marijuana were the most frequently used, and preferred, substances in both groups, the Type-I group showed greater numbers of individuals who preferred alcohol only. Implications: Results suggest that, although Cloninger's Type-II profile was found among these multiple-problem adolescents, attention towards characterizing subtypes of early onset substance abusers is important.

PSYCHOLOGICAL CORRELATES OF SUBSTANCE USE IN CONDUCT DISORDERED YOUTHS: GENDER DIFFERENCES

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There may be treatment implications if psychological correlates of substance dependence symptoms (SD) differ in male and female youths with Conduct Disorder (CD). HYPOTHESES: While exploring other relationships, we developed these hypotheses: 1) total CD symptoms and "aggressive" CD symptoms will relate to SD in males and 2) negative self-concept, empathy, and depression will relate to SD in females. METHODS: With standardized interviews and questionnaires we measured self-reported SD, empathy, depression and self-concept in 78 male and 78 female adolescents with comorbid CD and substance use diagnoses. We also separately considered number of "aggressive", "non-aggressive", and total CD symptoms. RESULTS: Males had significantly ($p<.05$) more SD, total, and "aggressive" CD symptoms and females had higher empathy scores. Only total CD (not "aggressive") related to SD in males ($r=.28$, $p<.01$), accounting for 6% of the variance after adjusting for socioeconomic status and race. In females, SD was associated positively with empathy ($r=.23$, $p<.05$) and negatively with self-concept ($r= -.38$, $p<.01$) but not with depression. Depression was highly correlated with self-concept in both genders ($r \geq -.62$, $p <.01$). Multiple regression of SD on these variables showed that negative self-concept ($p<.002$) and empathy ($p<.07$) together significantly accounted for 12% of the variance in SD in females after adjusting for race and socioeconomic status ($R=.50$, $p<.0002$). CONCLUSIONS: Male and female adolescents with CD differ in their psychological correlates of SD, suggesting different treatments. For males only total CD symptoms related to SD. The combination of empathy and negative self-concept best predicted SD in females. ACKNOWLEDGEMENTS: Supported by NIDA grants DA06941 and DA09842.

COVARIANT DEVELOPMENT OF DRUG ABUSE, BODY, INTELLIGENCE, PERSONALITY, AND PSYCHOPATHOLOGY AS A FUNCTION OF TESTOSTERONE: A LIFE-TIME PREVALENCE STUDY OF 4.429 ANDROTYPED MALES

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This study examines the development of drug abuse/dependency in terms of The General Trait Covariance (GTC) model (Nyborg 1994a). The full GTC model predicts body, brain, intellectual, and personality development from genes, sex hormones, and experience. The shorter version of the model used here relates plasma testosterone to drug-abuse/dependency and general development. The subjects (4.429 middle-aged US male veterans, CDC 1988) were classified into four groups: 1) no drug abuse (Never), 2) abuse in the military only (OnlyMil), 3) abuse only after active service (NowOnly), or 4) abuse during and after service (Sustained). Discriminant function analysis suggested that plasma is a powerful discriminator variable among the groups, so the average for the four groups was determined. The GTC model was then used to predict the most likely development from their androtype, and the predictions were compared to actual data on the bodily, intellectual, personality, and psychopathologic characteristics of the different groups. The Never group has "t" a value identical to the population average, which classifies them as androtype A3. Both OnlyMil and NowOnly groups had above average values, so they classify approximately as androtype A4s. The Sustained group had the highest mean "t" value, approaching that of androtype A5. From previous studies (*e.g.* Nyborg, 1994a) we knew, that high "t" androtype A5 males tend towards low IQ, brief education, high Extroversion, Neuroticism, Psychoticism, Depression, Hypomania, and delinquent behavior, as compared to low "t" Als. We therefore expected increasingly lower IQ, shorter education, a more vulnerable personality, and more psychopathological symptoms as plasma "t" increases in the drug abuse groups, and this was found. In general, the higher the "t", the lower the body mass index and intelligence, the lesser education, the more personality and psychopathology problems, and this was seen most clearly in the Sustain group. Findings were interpreted in terms of physicology. Physicology sees humans as complex carbon-based molecular organizations whose development and behavior depends on DNA instructions and on how these instructions are modulated by, say, hormones in the nonlinear dynamic interaction with an entirely physico-chemical environment (Nyborg 1996). Drug abuse/dependency reflects, in this view, a combined intrasystemic gene - endocrine disturbance with an affect on body and brain development promoting maladaptive responses to intra - extrasystemic mismatches.

FACTORS ASSOCIATED WITH ADDICTION SEVERITY AND CRIMINALITY AMONG FEMALE OFFENDERS

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Effective treatment of drug impaired female offenders is critical. An important part of developing treatment interventions is an understanding of the factors associated with both addiction and criminality in women. In this study, we assessed 300 female offenders admitted to a residential drug treatment center. The majority (62%) abused cocaine, 48% had a psychiatric diagnosis of ASPD, and 57% PTSD. Family background showed that 86% had a family history of substance abuse, 18% of psychiatric disorders in their family, and 26% of criminal activity by a family member. Physical abuse as a child was reported by 73% and 55% had been sexually abused. Sexual and physical abuse, as well as PTSD and having a family history of psychiatric disorders, were highly associated with both medical and psychiatric problems (using the Addiction Severity Index). Sexual abuse, physical abuse, and having a family member who was a criminal, were associated with criminality.

Clients, not surprisingly, were characterized by extreme problem severity in most areas of their lives. It appears that antecedents of drug abuse or dependence and criminality include both environmental (personal history) and genetic (family history) contributions among this population. ACKNOWLEDGEMENTS: This work was supported in part by the Colorado Dept. of Safety, Drug Control & System Improvement Program, Bureau of Justice Assistance, #95-DB-15-4.

GENDER, AGES, AND ETHNIC DIFFERENCES IN DRUG USE AND CRIMINAL ACTIVITY INITIATION

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Criminal and drug histories were elicited from a sample of 717 current drug users who were originally accessed in hospital emergency rooms, sexually transmitted disease clinics, and jail booking areas in Los Angeles County. The sample consisted of 52.9% African American, 25.2% Hispanic/Latino, and 18% white participants, with 65.1% men. More men (95.3%) than women (86.4%) reported having been arrested; men had also been arrested more times, a mean of 15.3 vs 10.1 for women. Age of first arrest was lower for men (16.5) than women (19.6), although mean number of convictions was similar for both at over six. By self-report, women had generated more income from crime ($13, 281) in the past year than men ($11, 187). Examining the sample by ethnicity, over 90% of all groups reported having been arrested. The Hispanic/Latino group had been arrested fewer times with a mean of 11.5 compared with over 14 for the other two groups. Mean age of first arrest was similar for all three groups (over 17).

The sample was divided in two ways: by mean number of non-juvenile arrests over the lifetime into a lower crime group (fewer than 13 crimes) and a high crime group (14 or more crimes) and by age of first use of an illegal drug into early initiators (at 15 years of less) and later initiators (16 and over at age of first use). Those who began drug use earlier were more likely to have high numbers of reported crimes.

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DIFFERENTIAL DRUG USE PROGRESSION PATTERNS AMONG THREE AGE COHORTS

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Differential drug use progression patterns were evaluated for a sample of 717 drug users originally screened and interviewed at selected sexually transmitted disease clinics, hospital emergency rooms, and jail booking areas in Los Angeles County. The sample was divided into three age groups: younger (18-29), middle (30-39), and older (40+). Mean age of the total sample was 32.1 years with 4 1% younger, 4 1% middle, and 18% older subjects. The age groups varied in their drug use patterns. The older group had far greater use of stimulants and heroin, the middle group was more likely to have tried powder cocaine or crack, and the younger group were slightly more likely to have tried marijuana and alcohol. Age of initiation was linearly related to age: the younger the subject, the lower the age of first use of each drug in question. Similarly, age of first regular use was lower for the younger groups. The total sample had tried an average of 5.5 illegal drugs over the life span, with a mean of five by the age of 29. The younger group had used 4.3 drugs, the middle group had used 5.6 drugs by the age of 29 and the older group five drugs by the age of 29. Time from first use to regular use for powder and crack cocaine was about one year for the total sample. For the young group the time to regular use was about one year for powder and .67 year for crack cocaine. The middle group took about one year to reach regular use and the older group took 1.5 years for powder and .82 years for crack regular use. The younger group had the least treatment experience, the lowest motivation for treatment scores, and was the most likely to live with other drug users. With the increasingly younger age of initiation and regular use of drugs, treatment targeted to the young is needed to access this group of dependent users.

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DRUG USE AND GENDER ROLE ORIENTATION OF MALE AND FEMALE COLLEGE STUDENTS

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Research suggests that the psychologically androgynous individual tends to be more healthy mentally than those who possess strongly masculine or feminine traits only (Spence & Helmreich 1980). Psychological androgyny refers to the possession of both masculine and feminine personality traits. This study attempted to add to what is known about the psychological advantages of androgyny by looking at the relationship between gender role orientation and drug use. Two hundred and eight male and female undergraduate students enrolled in General Psychology classes were surveyed using the Personal Attributes Questionnaire (Spence & Helmreich 1974) and the revised Drug History Questionnaire (Sobell *et al.* 1995). It was hypothesized that androgynous persons of both sexes would indicate less experience with illicit drugs than those with traditional gender role orientations. Results showed that gender role orientation was unrelated to the use of alcohol, nicotine, caffeine, prescribed, over-the-counter, and illicit drug use. However, there was a positive correlation between masculinity and illicit drug use among female college students. The most common drugs used were alcohol, caffeine, and over-the-counter medicines regardless of gender role orientations. Of interest, males scoring low in masculine and feminine traits smoked more marijuana than all others.

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ESTIMATES OF GENETIC INFLUENCES ON ILLICIT DRUG USE IN MALES AND FEMALES

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Information on illicit use of sedatives, stimulants, opiates, hallucinogens, and cannabis was obtained by questionnaire from a sample of twins, recruited from 16 addiction treatment centers in Minnesota (Pickens *et al.,* 1991). Subjects were monozygotic male (MZM) and female (MZF) (91 and 50 pairs), dizygotic male (DZM) and female (DZF) (105 and 46 pairs), and dizygotic opposite-sex (DZ-OS) twins (101 pairs). Most probands met DSM-III criteria for alcohol abuse/ dependence. Prevalence of illicit drug use was 60% for male, and 72% for female probands, and 41% and 39% for male and female co-twins. Problem use was reported by 47% of male, and 60% of female probands, and 25% of male and 22% of female co-twins. The most frequently used drug for males was cannabis (51% of probands; 36% of co-twins). For females, both stimulant (57% in probands; 25% in co-twins) and cannabis use (53% in probands; 33% in co-twins) were frequently reported. Tetrachoric correlation coefficients were calculated and heritability estimates were obtained by taking $2*(r_{MZ}-r_{DZ})$ for the same-sex twin groups. Genetic influences were found to contribute to use of any drug type, as well as problem use in males. In females, use of sedatives, stimulants, cannabis, as well as any illicit drug use showed a genetic influence. Environmental factors, not shared by family members appeared stronger in female than male drug use. Comparison of same-sex dizygotic male and female twin groups with the opposite-sex dizygotic twin group suggested gender-specific genetic/environmental influences on drug use.

REFERENCE: Pickens, R.W.; Svikis, D.S.; McGue, M.; Lykken, D.T.; Heston, L.L.; and Clayton, P.J. Heterogeneity in the inheritance of alcoholism: A study of male and female twins. Arch Gen Psychiatry 1991 48: 19-28.

DRUG ABUSE TREATMENT ACCESS AND UTILIZATION: GENDER DIFFERENCES IN THREE HIGH-RISK SAMPLES

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Current drug users were recruited from emergency rooms, sexually transmitted disease clinics and jails in Los Angeles County. In-depth interviews on drug use and treatment utilization were completed with 717 subjects (35% women). Mean age for both genders was about 32 years. Women, in general, had a higher rate of experimentation with heroin and powder cocaine. More men had tried other drugs. Mean age of first use of stimulants, heroin, and crack was higher for men and for other drugs was higher for women. Men and women were similar in age of first regular drug use and days of substance use in the previous month. More women (56%) than men (45%) reported having been in drug treatment. Women were also more likely to seek help from sources other than formal treatment programs, except for work-site help, a source more approached by men. Treatment seeking women had sought but not received drug treatment at a higher rate (18%) than men (11%). The main barriers to treatment were "unable to pay" and "no slot available" which were equally important for both groups. "Didn't meet eligibility criteria" was more a barrier for women (36%) than men (22%). A major difference between women and men is that women are much more likely to follow through in treatment seeking. In this sample, 9.64% of women and 31.80% of men had considered seeking help for their drug problem but did not. Women were more likely to attribute this to "long waiting list" and "need for childcare", while more men reported as reasons "would lose pay from work" and "would be out of school" among other reasons. Drug users continue to have access barriers and unmet service needs. Gender differences must be considered when attempting to improve access and utilization of treatment. **ACKNOWLEDGMENTS:** Supported by NIDA grant DA 07382

COMPARISON OF MEN AND WOMEN RESPONDING TO COCAINE RESEARCH RECRUITMENT

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This study sought to compare gender differences in a non-treatment sample of crack cocaine users. Data was collected from initial screening interviews of men and women responding to cocaine research recruitment in a midwest urban environment over a two-year period. The telephone screening used a structured questionnaire inquiring about drug use as well as health, psychiatric and criminal histories. Women were asked additional questions about their reproductive health. Female respondents (n=88) were age- and race-matched with men interviewed over the same time period, for a total sample size of 176. The majority of the sample were black (60%), and mean age was 33 yrs. Basic demographics were similar for both genders. Respondents on average reported 13 yrs of education, had first used cocaine at age 24, and currently smoked 2 g cocaine/day for 5 days/week. Women were found to have significantly higher rates of cigarette smoking, headaches and suicidal ideation, and reported significantly more emergency room visits following crack use, than did men. Crack use had negatively affected the value systems of nearly all respondents (94%), and significant numbers of both men and women reported involvement with sex-for-crack bartering. Equal numbers of both genders had been convicted of a crime, with significantly fewer women reporting crimes involving violence. Although 56% of women reported exchanging sex for crack, two-thirds of women able to become pregnant used no method of birth control, the use of barrier methods was infrequent, and 42% acknowledged using cocaine during pregnancy. These data indicate that while there do not appear to be gender differences in patterns of crack use in this sample, community outreach and intervention programs may benefit from addressing some of these gender-specific behaviors associated with crack use. **ACKNOWLEDGEMENTS:** Supported by NIDA grants R01-DA 05844, P50 DA 09259 and T32 DA07097

BARRIERS TO ENGAGING PARTNERS IN WOMEN'S SUBSTANCE ABUSE RECOVERY

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Evidence indicates that women's drug treatment outcomes are improved by involving their partners in services (Higgins *et al.,* 1994). However, little is known about male partners of female substance abusers and efforts to engage them constructively remain largely unsuccessful. Interviews are being conducted with female clients and their partners in New York's Family Rehabilitation Program, a multi-site, comprehensive services program for families with cocaine-exposed infants, which includes low caseloads, case management, home visits, outpatient drug treatment, and on-site child care. Preliminary analysis yields a profile of the significant others and suggests reasons why outreach efforts to partners may be frustrated. While only about one half of these men report currently using drugs and/or alcohol, most have extensive drug use in their past and little or no successful experience with the treatment process. The extent of support they give their female partners in treatment is limited. Those who do encourage their partners in treatment often do so to avert having the children removed by child protective services and to avoid the cultural stigma attached to being with a crack-addicted woman. These preliminary findings indicate that men play a complex role in women's drug treatment process, and that partners' own drug use is not the only explanation for their lack of support. More must be learned about how to engage male partners constructively in women's treatment.

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WITH THEIR CHILDREN AT THEIR SIDE: A COMPREHENSIVE DESCRIPTION OF WOMEN ENTERING METHADONE MAINTENANCE

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Although gender differences in the nature of opioid dependence can be traced back to the turn of the century, there have been few comprehensive descriptions of contemporary cohorts of women seeking treatment for heroin addiction. Consequently, this study was designed to characterize a cohort of women entering methadone maintenance, document their responsibilities as parents, and quantify potential threats to the well-being of their children. Admission data collected from 164 subjects indicated that, more often than not, women entered treatment struggling with their addiction, obligations to care for at least one minor child, and an array of related problems. Analysis of these problems from a developmental perspective documented the presence of multiple threats to normative development in the lives of 181 children living with their opioid-dependent mother. Consistent with previous calls for more family-oriented approaches to treatment, the results of this study suggest that intervention designed to better meet the needs of opioid-dependent women must acknowledge their status as parents and address concurrent problems that represent threats to the well-being of both the women and their children. Given the multiplicity of chronic risk in the lives of the children living in the inner city with an opioid-dependent mother, methadone maintenance programs may also be the most appropriate setting to provide ancillary services designed to promote positive development in children of all ages.

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PREDICTORS OF PROBLEMS AMONG CHILDREN OF DRUG ABUSERS

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Children of drug abusers (CDAs) are at greater risk for behavioral/emotional problems than matched comparison groups. However, not all CDAs show problems. To identify predictors of poor outcomes among children of drug abusers (CDAs), we assessed children's problems via standardized rating forms from: (I) a cocaine or opiate dependent parent; and (2) the child's teacher. Sites included Burlington, VT, Houston, New Jersey, and Toronto. 150 patients completed the Child Behavior Checklist (CBCL) about 253 children. Predictors included parental drug of abuse, site, gender of child and parent. We found significant effects of site only on Social Problems, with higher scores for NJ subjects than Texas or Canadian subjects. We found signficicant effects of ethnicity on Delinquent and Aggressive Behavior, with higher scores for Caucasian than non-Caucasian subjects. We found a main effects of parent gender on Somatic Complaints, with higher scores for children of female than male drug abusers. In addition, parent gender x drug of abuse interactions were significant for Somatic Complaints and Aggressive Behavior. For Somatic Complaints, children of female opiate abusers scored higher than children of male opiate abusers. For Aggressive Behavior, children of female cocaine abusers scored higher than children of male cocaine abusers. The same patterns were found for teacher reports on these two syndromes, but the differences were not significant. These findings on Somatic Complaints are consistent with research showing more psychiatric problems, especially somatization, that do not improve with buprenorphine treatment among female than male opioid abusers. In addition, each of the ASI scales was significantly correlated with children's Anxious/Depressed scores, and, despite their intercorrelation, several ASI scales accounted for unique variance in CBCL scores, including the Family/Social scale which predicted six of eight child syndromes.

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SAMPLE BIAS IN CLINICAL DRUG ABUSE RESEARCH

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We evaluated possible sample bias among 3119 research applicants at a drug abuse research center who passed an initial telephone screen and attended their first recruitment visit between January 1992 and August 1995. Applicants' sociodemographic (age[mean 33.1 years], race [two-thirds African-American], sex [two-thirds male]), psychological (Shipley verbal raw score, SCL-90R general severity index), and current (30-day) self-reported substance use characteristics were used in a step-wise logistic regression model (maximum likelihood estimation method, SPSS 6.0 program package) predicting entry into any research study and into a treatment (vs. non-treatment) study. Forty six and six percent of applicants were admitted to a research study, with non-cigarette smoking male cocaine users more likely than others to be admitted. Younger, non-heroin using males with less psychological distress and higher Shipley scores were more likely than others to enter non-treatment studies. Univariate analyses found that users of cigarettes and alcohol were less likely than non-users to be admitted to a study. These findings are generally consistent with the explicit eligibility criteria of the applied-for research studies, and suggest that there is substantial potential for selection bias during recruitment of research subjects. One limitation of these findings is the substantial overlap between non-treatment and residential studies, with the latter tending to exclude women with child care responsibilities.

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SUBSTANCE USE AND ITS RELATION TO ADVERSE WORKING CONDITIONS

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We hypothesized that nurses who encounter difficult working conditions would be more likely to use substances than colleagues without similar work demands. In addition, social role theory suggests that among women, increased family/home demands create role strain, and could lead to increased use. Adverse conditions included shift rotation, weekends on, shift length (>8 hours) and working overtime. These variables were also combined into an index of adversity. Past year substance use included street drugs, prescription-type, alcohol use (5+ drinks/occasion) and cigarettes (1/2 pack/day). An anonymous survey with up to six contacts was mailed to a random sample of nurses (78% response rate, n=4436). Those currently employed (n=3917) were included in this analysis. Work schedule characteristics, which objectively measure a time constraint or pressure, indicated that the more adverse one's schedule, the greater the likelihood of substance use (e.g.: Alcohol OR=1.85; 95% CI: 1.53-2.22). In multivariate models, demographics were more strongly related to use than the working conditions. Further exploration of the demographic influences as they relate to role strain among women, found the odds of alcohol use for adverse conditions increased among married women with children under age four (OR=2.07; 95% CI:1.26-3.39). Whereas among single mothers, adverse conditions reduced the odds of alcohol use (OR=0.51; 95% CI:0.10-2.53). Alcohol use among men was consistently associated with working conditions, regardless of marital or family status.

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SPECIFICITY OF FAMILIAL TRANSMISSION OF ALCOHOL AND DRUG DEPENDENCE

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A structured interview (Family History Interview) was administered to 142 opiate-dependent probands (60% male, 56% African American, mean age 37.5 yrs) to obtain DSM-IV alcohol and drug dependence diagnoses in first-degree relatives $\geq$ 18 years of age (n=708). Prevalence of drug and alcohol dependence was compared in siblings as a function of parental alcohol dependence. Substance abuse was more common in parents and siblings of probands than in the general population (National Comorbidity Survey, adjusted for age and racial characteristics of sample). Alcohol dependence was present in 13% of mothers and 42% of fathers, with drug dependence present in 3% of mothers and 4% of fathers. While male and female probands did not differ significantly in severity of drug dependence, female probands were 3 times more likely to have parental alcohol or drug dependence than male probands. Alcohol dependence was present in 20% and drug dependence in 23% of male siblings, and alcohol dependence was present in 9% and drug dependence was present in 12% of female siblings. Female probands reported more affected female siblings for both alcohol and drug dependence. To examine specificity of familial transmission, rates of alcohol and drug dependence were compared in siblings of probands with and without parental alcohol dependence (in probands having siblings). Parental alcohol dependence increased risk for both drug and alcohol dependence in siblings. Paternal alcohol dependence increased sibling risk for alcohol dependence by a factor of 2.4 (CI 1.4-4.2) and drug dependence by a factor of 2.7 (CI 1.3-5.5). Maternal alcohol dependence increased sibling risk for alcohol dependence by a factor of 2.7 (CI 1.4-5.2) and drug dependence by a factor of 3.3 (CI 1.8-6.1). The results suggest lack of specificity in familial transmission of alcohol and drug dependence, with familial factors related to alcohol dependence acting to 'enhance risk for both alcohol and drug dependence in relatives of opiate-dependent individuals.

SUBSTANCE ABUSE AND ITS TREATMENT: A SOCIAL CONTROL PERSPECTIVE

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This paper posits that substance abuse is an intentional or unintentional escape from social control on the part of users. Treatment, in contrast, is an intentional restoration of social control on the part of authorities. Social control is defined as a normative and behavioral restraint upon individuals for a socially appropriate level of attachment and regulation. Over-attachment subjects individuals to group pressure while lack of attachment generates alienation and suicidal tendencies. Over-regulation leads to depression, whereas lack of regulation results in anomie and disposition to violence. These four states derived from the two social control dimensions provide motivation for drug use and abuse. As dependency develops, addicts experience not only loss of social control but also detachment of body from soul/mind and lack of regulation of the latter over the former. On the part of society, individual experiences of loss of control always mean and have to be compensated with coercive control of crimes and social problems. Treatment, correspondingly, begins with medical control to restore equilibrium or a proper level of attachment and regulation between body and soul/mind. Therapeutical control is then applied to rebuild self-control for the internalization of dominant religious or ideological values. Family and group sessions are used to establish attachment to primary and secondary relations. Vocational training is provided to introduce disciplinary control of work. As former addicts come back to a socially-functioning life, society not only gains positive social control but also saves cost from negative control of law enforcement or punishment. This paper sheds new light on the nature and process of substance abuse and its treatment, and helps better understand their social and political implications in a larger political-economy context.

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EFFICACY OF COERCIVE AND NON-COERCIVE PRESSURES TO ENTER COCAINE TREATMENT

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This study investigated the relative influence of coercive and noncoercive pressures to enter cocaine treatment on tenure and abstinence (for operational formulations and assessment procedures, see Marlowe *et al.* in press). Stepwise multiple regression analyses (N = 190) revealed that the total number of perceived treatment-entry pressures was positively related to the number of counseling sessions attended ($R=.16$, $p<.05$) and to the total number of cocaine-free urines provided ($R=.16$, $p<.05$). The number of perceived noncoercive pressures (a desire to obtain rewards from significant others and to improve one's self-image) was positively related to weeks of enrollment in treatment ($R=.21$, $p<.005$) and to the largest number of consecutive cocaine-free urines provided ($R=.17$, $p<.05$). Coercive pressures did not predict treatment tenure or outcome. The data suggest that coercion plays a role in initiating treatment entry, but aversive control is less likely to bring about or maintain treatment goals. Clinicians should therefore focus on positive contingencies that naturally result from counseling attendance and drug abstinence; in particular, improvements in clients' social relationships and self-esteem.

REFERENCES

Marlowe, D. B.; Kirby, K. C.; Bonieskie, L. M.; Glass, D. J.; Dodds, L. D.; Husband, S. D.; Platt, J. J.; and Festinger, D. S. Assessment of coercive and noncoercive pressures to enter drug abuse treatment. Drug Alcohol Dependence

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DRUG TREATMENT PROGRAM ADMINISTRATORS' ATTITUDES ABOUT CLIENT RELAPSE AND TREATMENT SUCCESS

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As part of a larger study on drug treatment process and program effectiveness, drug treatment program administrators were interviewed regarding their attitudes toward "partial success" during client treatment. Partial success was defined as "such client outcomes as the client decreases his or her substance abuse or is sober for increasingly larger periods of time." Administrators were asked if they considered the above client outcomes a partial success and were asked to explain why. Adminstrators' responses will be presented in light of program modality and administrators' years in the treatment field, gender, ethnicity, income level, recovery status, level of training, therapeutic style, optimism, well-being, self-efficacy, and beliefs about client changeability.

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SITUATIONAL CONFIDENCE QUESTIONNAIRE SCORES AS PREDICTORS OF OUTCOME IN THE TREATMENT OF COCAINE DEPENDENCE

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Scores on the Situational Confidence Questionnaire (SCQ, Annis, 1984) predict outcome in the treatment of problem drinking, opiate abuse and cigarette smoking. We examined whether intake scores on a version of the SCQ short-form modified by us to address cocaine use predicted abstinence during outpatient behavioral treatment for cocaine dependence. Patients participating in a clinical trial evaluating the efficacy of voucher-based reinforcement therapy completed the SCQ during their first week of a 24-week treatment program. Patients were randomly assigned to either a treatment group that received vouchers contingent on cocaine abstinence or to a yoked control group. SCQ scores at intake and continuous weeks of cocaine abstinence were not significantly related overall ($r=.32$, $p=.07$), but there was a significant interaction between treatment group and SCQ scores ($p=.03$). There was no significant relationship between SCQ scores and cocaine abstinence in the yoked control group ($r=-.09$, $p=.64$), but there was a significant positive relationship between SCQ scores and abstinence in the contingent voucher group (r-.45, $p=.02$). These results suggest an interesting relationship between intake confidence levels and systematic positive reinforcement that merits further investigation. Elucidating this relationship could contribute to our understanding of the predictive utility of the SCQ and the efficacy of contingency-management interventions.

PATIENT TREATMENT CHOICE AND COMPLIANCE: DATA FROM A SUBSTANCE ABUSE TREATMENT PROGRAM

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It has been suggested that patient compliance could be improved by providing for patient participation in the medical decision-making process. The current study, conducted with treatment-seeking cocaine dependent persons, who are known to be difficult to retain in treatment, was designed to test the hypothesis that patients given the opportunity to choose between treatment approaches would do better than patients randomly assigned to the same approaches with respect to treatment retention and nine-month outcome. Subjects included 34 patients who voluntarily chose to enter individual therapy, 1 hour per week (IND,) and 33 who chose intensive group therapy 3 hours, 3 times weekly (INT). There were no significant differences between these two groups on demographic, personality, or addiction severity variables as well as treatment retention or nine-month outcome. Comparison with samples of 30 patients who had been randomly assigned to IND and 30 to INT did not confirm the hypothesis that patients who chose their treatment would, a) remain in treatment for longer periods of time, and b) manifest improved nine-month outcomes. Several interesting motivational issues are raised.

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RELAPSE TO COCAINE USE MAY BE PREDICTED IN EARLY ABSTINENCE BY LOW PLASMA DEHYDRO-EPIANDOSTERONE-SULFATE LEVELS

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Blood and 24 hour urine samples were collected from 37 recently abstinent cocaine-dependent males (DSM III-R) and 29 matched controls in order to determine whether hormone levels measured during early abstinence would predict subsequent relapse to cocaine use. The study was conducted as part of a six month longitudinal assessment of the neuropsychological effects of chronic cocaine. Cocaine patients manifested higher mean plasma cortisol and 24 hour urine free cortisol levels (13.80 ± 2.89 µg/dl and 66.03 ± 3 1.04 µg/dl) when compared to the control subjects (10.91 ±2.74 µg/dl and 30.12 ±13.77 µg/dl), with differences demonstrated by 2-tailed Student t, with unequal variance at p=0.0018 for the plasma levels and p=0.000006 for the 14 hour urine levels. The cocaine and control patients did not significantly differ in their first day abstinence plasma prolactin levels (8.61 ± 2.63 ng/ml and 10.51 ±3.75 ng/ml). Conversely, lower mean plasma levels of the sulfate metabolite of dehydro-epiandosterone (DHEA-SO_4) were found in seven subjects who subsequently tested positive for BE within 45 days (213.1± 54.6 ng/ml), and in the 15 who dropped out within 45 days (179.0 ± 80.8 ng/ml) when compared to the 25 subjects (308.5 ± 106.8 ng/ml) who remained abstinent for at least 45 days (p=0.0092, 2-tailed Student t, unequal variance), and the 10 (346.9 ± 153.0 ng/ml) who remained abstinent for 90 days (p=0.0271, 2-tailed Student t, unequal variance). These preliminary findings suggest that cocaine patients in early abstinence manifest increased circulating cortisol levels and that cocaine patients with low DHEA-SO_4 levels during early abstinence may be at increased risk to relapse to cocaine use. Patients with an increased risk to relapse to cocaine use may comprise an important target population for medication and other treatments.

TYPE 1 ERROR RATES IN LONGITUDINAL STUDIES WITH MISSING DATA

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Missing data occur in nearly every study evaluating the effectiveness of proposed substance abuse treatments. Patients often miss clinic visits, fail to give urine samples when required, or simply drop out of study. Missing data present a particularly difficult statistical problem for analysis of longitudinal data. Until recently, missing data were handled by deletion or various methods of data imputation, each with known problems, such as producing biased results (Rovine and Delaney 1990). Several researchers (Dempster, *et al* 1977; Little and Rubin 1987; Marini, *et al* 1980) have summarized and extended theoretical foundations for calculating maximum likelihood estimates under conditions of missing data. Inferential tests associated with these analyses are based on large sample theory. Evaluation of their validity for small sample sizes is extremely limited. Data were presented from Monte Carlo analyses of Type 1 error associated with Complete cases/List-wise deletion Repeated Measures ANOVA/ANCOVA, ANOVA on slopes, ANCOVA on slopes, and Random Regression analysis. The pattern and degree of missing observations, and sample size were assessed for their effects on Type 1 error in a two-group, five repeated measures design. Type 1 error was presented for three linear dropout rates (20%, 40%, and 60%), three missing data rates (10%, 21%, and 33%), and two sample sizes (n+15 and 45 per group). Based on these analyses, we conclude that Maximum Likelihood REML statistics need to be corrected for small samples (Schulchter and Elashoff 1990.) Type 1 Error under missing patterns are closer to nominal alpha than under drop out patterns. Additionally, under conditions where data can be considered missing at random. Type 1 error for list-wise deletion analyses was comparable to that for Random Regression. Type I Error for ANOVA or ANCOVA based on slopes are more conservative than rates for analyses based on endpoints or Random Regression with slopes. This difference is most pronounced in the small sample drop out pattern condition.

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WHY CRACK TREATMENT PROGRAMS FAIL: THE SPECIAL HABILITATION NEEDS OF URBAN CRACK USERS

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To confirm anecdotal evidence of greater psychiatric, social, and psychological deficits among crack users, those applying for admission to a NIDA-demonstration project were compared with methadone patients in a concurrent NIDA project. Demographically, the two populations were alike, although unlike the US as a whole. Methadone patients had a greater number of treatment episodes, likely due to their being older. ASI composites also indicated agreement, except for legal status, where methadone patients had a higher level of current legal concerns, possibly due to longer use or the need for more money to maintain use of opiates and possibly the extreme poverty in the city where the crack sample resides. One area of difference between the two populations was psychiatric status (SCL-90). Consistently, the methadone sample scored 1 SD below the mean for psychiatric outpatients and the crack sample scored 1 SD above the mean. Females in both samples showed more impairment. These findings confirm reports of high levels of impairment among crack and heroin addicts. They are poorer, less well-educated, more likely to be unmarried, and largely unemployed. These deficits should be simultaneously addressed in treatment, so that true rehabilitation can occur. For crack addicts, however, the high level of psychiatric impairment may interfere with successful integration of these treatment efforts. Thus, attention to psychiatric deficits is called for SO that treatment can be effective.

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ALEXITHYMIA IN THE TREATMENT OF COCAINE ABUSERS

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Some clinicians have proposed that alexithymia, a difficulty in differentiating and communicating feelings, may be an indicator of a subject's ability to successfully complete treatment, and may subsequently play a role in determining treatment specificity in cocaine abusers. Measuring the prevalence of alexithymia and associated clinical and demographic variables in a crack abusing population, at baseline and over time, may help to validate and further delineate effective treatments. To this end, the Toronto Atexithymia Scale (TAS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and the Addiction Severity Index (ASI), were administered to 275 subjects (75.9% male) crack cocaine abusers (ages 20-48) who were enrolled in a randomized, pharmacological trial of a theorized anti-craving drug for the treatment of cocaine dependence. One hundred and nine subjects completed the 12-week dosing trial. For the 275 subjects, the mean time for abstinence prior to initial dosing was 6.29 days ± 9.47 days. There were no significant differences between sex, level of depression or anxiety, or severity of craving at baseline for the completers vs droppers. Analysis of variance found no significant differences between the TAS scores of completers vs. droppers (67.45±11.74 vs. 68.13±13.28). Additionally, a chi square test for association between completion status and alcxithymia (TAS>74) was not significant. However, a repeated measures analysis of TAS over the 12-week dosing regimen showed a significant linear decreasing trend in the mean TAS scores for the completers ($p \leq 0.018$). Although these interm results do not support an association between alexitnymia and an individual's ability to complete a treatment regimen, a final determination cannot be made until the study's end. However, it should be noted that the process of completing a treatment program does seem to have the effect of decreasing alexithymia levels. Future research will hopefully better elucidate this association.

DEFINING AND PREDICTING "RELAPSE" FOLLOWING TREATMENT OF COCAINE DEPENDENCE

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Relapse continues to be a key outcome measure in treatment evaluation research, despite a lack of consensus regarding its operational definition. The objective of this report is two-fold: (1) to empirically compare three models of defining "relapse", and (2) to examine the consistency of relapse correlates across the three definitions. Thirty-two cocaine dependent adults received eight weeks of outpatient relapse prevention skills training therapy then were re-assessed at seven time points over a one year follow up period. Separate survival curves were constructed for three definitional models of relapse. Model 1 defined relapse as **any** occurrence of cocaine use. This model is most conservative, and considers complete abstinence as the index of treatment effectiveness. Model 2 defined relapse in relation to baseline behavior, thus attempting to distinguish between lapse and relapse. Using this definition, relapse occurs when the frequency of cocaine use is greater than 50% of baseline frequency. Model 3 proposes a multidimensional definition of relapse, with equal weighting given to domains of substance use and psychosocial functioning (*e.g.,* employed days, family conflict, illegal activity). As expected, the three curves were distinctively different in shape ($X^2 = 12.1$, $p<.002$), with Model 1 producing the sharpest decline in survival. Fewest "relapses" were found using Model 2. Hazard function analyses showed that for Model 1 and Model 3, the first 24 weeks following treatment represent the highest relapse risk periods. For Model 2, there was a slight peak in the hazard rate between 24-36 weeks following treatment. The significance of relapse predictors varied as a function of definitional model. For instance, post-treatment self-efficacy ratings correlated with latency to relapse for Model 1 only, whereas ASI employment severity scores correlated with latency to relapse for Model 3 only. In summary, reliance on a single definition of "relapse" is likely to limit the amount and meaningfulness of the treatment outcome information,

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FACTORS AFFECTING LENGTH OF STAY (LOS) ON AN INPATIENT DETOXIFICATION UNIT

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Hypothesis: Clinical and nonclinical factors affect length of stay (LOS) in noncapitated health systems. Identifying these factors can target patients requiring extended or intensive treatment, as well as expediting the transfer of healthier veterans to less structured, and less costly, treatment settings.

Procedures: Diagnostic and demographic data were collected from 428 voluntary admissions to an inpatient detoxification unit. The authors used student t-tests, chi-square analyses and one-way analysis of variance (anova) techniques to determine which factors influenced LOS. The strongest independent predictors were then entered into a multiple regression model to determine how much variance in LOS could be accounted for and which factors retained their predictive power with competing factors taken into account.

Results: Age ($r=.1185$, $p<.014$), differing aftercare plans ($F=12.42$, $df=4$, $p<.01$), schizophrenia ($t=2.16$, $df=426$, $p<.05$), HIV status ($t=-2.52$, $df=426$, $p<.05$), and AMA discharges ($t=12.29$, $df=97.71$, $p<.01$) all significantly altered the LOS on the detox unit. However, when viewed collectively, these factors accounted for only 19% of the variance in LOS ($R^2=19$). These findings suggest that while LOS may be unpredictable, certain variables can be used to determine which patients will require lengthier, costlier services.

A COMPARISON OF THREE METHODS OF MEASURING THE TYPE AND QUANTITY OF TREATMENT SERVICES

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This study examined three methods of quantifying the type and amount of services provided in a publicly funded methadone program: (1) patient interview by the Treatment Services Review (TSR); (2) counselor interview by the Counselor Services Interview (CSI); and (3) data abstraction from clinical records (REC). Prior to the study, satisfactory inter-rater reliability was found between the trained interviewers across each method. A total of 50 patients were followed over 28 days to assess the services received/provided within the program. Weekly interviews were conducted with both counselors and patients, while record abstraction was completed one month after the 28-day period. Pearson Correlation Coefficients were calculated among the three methods of data collection, and examined five areas of service provision: medical, employment, drug, family, and psychiatric. Moderate correlations were found between the CSI and REC in the employment (.29), drug/alcohol (.36), family (.48), and psychological services (.33). Only psychological services (.42) yielded moderate agreement between the CSI and the TSR. Finally, only employment services (.48) were correlated between the REC and TSR. Regarding quantity of services, more total minutes of services were documented in the records (228) than either the TSR (182) or CSI (193). Post hoc focus groups with the counselors and patients noted two important factors: (1) counselors reported an "administrative burden" which reduced the quality of record notes and a "rounded-up" amount of time spent with patients; (2) counselors and patients both reported few problem specific counseling sessions focused on a single "type" of problem, but more sessions focused on the general monitoring of the patients' functioning.

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CLASSIFICATION AND REGRESSION TREES IN SUBSTANCE ABUSE RESEARCH

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We report on continuing work to develop and refine statistical tools for use in the analysis of studies of substance abuse. In this work classification and regression trees are explored and illustrated as methods applicable to problems of understanding results from clinical trials. Decision-tree based methodology has received little attention in substance abuse research and yet it may prove well-suited to such work. Advantages include the fact that results are easily interpreted, interactions are automatically incorporated, and mixtures of continuous and categorical data as well as missing data are efficiently handled. Recent work has extended these methods to longitudinal data and capturing prototypical group profiles. The use of decision trees for the detection of variables which may be important facets for patient-treatment matching is one such application. The main disadvantages include the chance of missing main effects and the replicability of results based on the initial data. Three examples; needle use, clinical outcome grouping, and time in treatment, are analyzed to demonstrate the procedures and to consider the disadvantages of this methodology.

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THERAPEUTIC APPROACHES: A SELF-ADMINISTERED ASSESSMENT INSTRUMENT

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As part of a general drug treatment counselor survey, a self-administered instrument was developed to assess counselors' therapeutic styles. The instrument assesses five major approaches to therapy: (1) the psychodynamic or interpersonal appproach, (2) the cognigive-behavioral approach, (3) the case management approach, (4) the family systems or dynamics approach, and (5) the twelve-step approach. For each therapeutic approach, three sets of items were developed, one for beliefs, and one each separately for practices in individual counseling and group counseling. Additional items were included which are not specific to these approaches but are popular beliefs and practices in the drug treatment field. The instrument was administered to 228 counselors in 46 drug treatment programs in Los Angeles County. These 46 programs were randomly selected to represent five major modalities including outpatient drug fee, inpatient hosptial, residential, methadone maintenance, and day treatment. Analyses of the internal consistency for each scales showed that Cronbach Alpha coefficients are mostly in the range between .6 to .8. Correlatons among sales were moderate within both beliefs and practices. There are also high levels of correspondence in scales measured between beliefs and practices. However, counselors' scores on various therapeutic approaches were not correlated with their self-reported formal training experiences and most counselors were eclectic or nonspecific except that counselors who were recovering substance abusers were more likely to believe and practice in the twelve-step approach.

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METHAMPHETAMINE USERS: PAYMENT TYPE, PSYCHIATRIC COMORBIDITY, AND RETENTION IN TREATMENT

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Methamphetamine dependence is a little studied and increasingly serious problem in the United States: Evidence of a relationship between payment type and treatment outcome would have important policy implications. Likewise, the prevalence of psychiatric comorbidity determines the need to make psychiatric care available to this population, and may influence treatment outcome. We conducted a review of the charts of 54 patients admitted to a private addiction medicine practice for treatment of methamphetamine dependence. Patients had a median age of 28 years (range: 14-46), were 33% female, 91% Caucasian, 60% unemployed, 26% percent had one or more additional substance abuse or dependence diagnoses (excluding nicotine dependence), and insufflation was the most common route of administration (50%), followed by intravenous (31%), and smoking (19%). Payment types (with median retentions in treatment, in days): out-of-pocket 46% (43), publicly funded (Medicare or Medicaid) 31% (30), and other third party insurance 22% (37), p=0.67. Current Axis I psychiatric comorbidity (with median retentions in treatment, in days): none 46% (29), major depression 26% (53.5), attention deficit disorder 15% (36.5), and any other psychiatric comorbidity 13% (29), p=0.76. Although payment type had no effect on retention, definitive assessment of this relationship will require a larger sample and prospective assessment of motivation, readiness for change, and social support, as these variables may differ substantially in patients willing to pay some or all of their treatment costs out-of-pocket. While no statistically significant differences were found with respect to psychiatric comorbidity, trends toward greater retention were evident in patients with major depression and, to a lesser extent, attention deficit disorder. The issue of psychiatric comorbidity urgently needs to be followed up as it has implications both for optimal psychosocial care and also for the choice of pharmacotherapies for clinical trials.

PERSONALITY AND SOCIAL CORRELATES OF COCAINE DEPENDENCE

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The relationship between the severity of cocaine dependence and personality factors such as sensation seeking, aggression, interpersonal sensitivity, and psychiatric symptoms such as attention deficit, depression, anxiety, obsessive-compulsiveness, somatization; and social factors such as social adjustment, criminal history, family history, drug-taking risk were examined in a sample of male veterans (N=239) with a mean age of 35 years. Canonical correlation analysis revealed three canonical variates. While general sensation seeking, experience seeking, verbal aggression, problem index for drug taking situations involving urges and pleasant times emerged as important personality and social variables, last cocaine use level, total number of cocaine grams used, age, number of times arrested and number of times incarcerated demographic, criminal and family history variables. The implications of these findings for prevention, treatment and future research have been discussed.

ASSESSING OUTCOMES WITH SPECIAL POPULATIONS: ADAPTING THE ADDICTION SEVERITY INDEX.

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The ASI was designed to capture genera1 information necessary to evaluate the nature and severity of patients' difficulties in seven areas: medical, employment, drug, alcohol, legal, family, and psychiatric. It's authors have always acknowledged the limitations of the instrument and encouraged additional data collection in the course of providing a thorough evaluation. Many requests have been made from substance abuse treatment providers for adaptations of the ASI. Adaptations, or ASI modules, and resulting norms are requested for clinical, cultural, research, accreditation, and funding reasons. ASI modules that incorporate JCAHO guidelines, a module sensitive to the Native American populations, and modules expanded to meet assessment needs for pregnant women, or incarcerated individuals are currently being completed. Modules have also been requested for the chronically mentally ill and for elderly substance abusers. Guidelines for making adaptations to the ASI including adding instructions, questions, and sections, norming new populations, and notes on the validity and reliability of ASI modules will be presented. The ASI-JCV (an ASI module designed to meet JCAHO criteria) and ASI norms collected with Native American's presenting for substance abuse treatment will be shown as examples.

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AN EXAMINATION OF THE ASI INTERVIEWER SEVERITY RATING SYSTEM

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Over the past few years, a number of treatment programs have used the interviewer severity ratings (ISRs) of the Addiction Severity Index (ASI) to help make treatment decisions. While we have published general guidelines for calculating ISRs, the scoring remains rather subjective. Therefore, in an attempt to reduce interviewer bias, we developed a computerized, algorithm for calculating ISRs. The aim of' this study was to compare the ISRs derived by trained research assistants, with the computerized algorithmic ISRs, against ratings derived by "expert" ASI trainers. Two recently completed studies provided us with 84 subjects. Using these data, ISRs were scored manually by two "expert" ASI trainers, a trained research assistant, and the computerized algorithms. ISRs range from 0 - 9 for each of the seven ASI profiles. There was good reliability between expert raters (mean = .85; range = .75 to .93), and also between the experts and the algorithms (means = .90 and .83; range = .70 to .96). Because some treatment programs use cut-off scores based on ISR, we conducted an experiment based on a policy were an assigned ISR of four or lower 'denies' treatment services. Examining ISRs across the four raters to determine the number of patients "denied" treatment indicated an occurrence of 8.7% or 51/588, where a patient was denied treatment, while the other raters would provide service. Based on the data obtained in this study, the computed algorithms yielded ISRs that agreed with the two expert ASI raters, yet yielded lower agreement when compared to the well trained research technician. Variability in the ISRs remained, even between the expert ASI raters. Although algorithmic ISRs can be computed the generally agree with the expert raters, the use of ISRs remains cumbersome because the numeric values obtained have little clinical utility.

RELIABILITY AND VALIDITY OF MEASURES OF STAGES AND PROCESSES OF CHANGE WITH STIMULANT USERS

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Prochaska and DiClemente's Transtheoretical Model of Behavior Change has received a great deal of attention in the addiction field. However, none of the current measures of Model constructs are designed specifically for cocaine and amphetamine users. After focus interviews with 20 stimulant users, revised versions of the University of Rhode Island Change Assessment (URICA), Processes of Change and Decisional Balance Questionnaires and a new Cartoon Stage of Change measure were administered at 3 time points (initial, one week, and three months) to 160 stimulant dependent people (primarily crack smokers) recruited from the street (68% male, 59% African American, 32% white non-Hispanic, 5% Hispanic, mean age - 37). Principal Components Analysis did not replicate four standard 8-item scales representing four stages on the URICA. The analysis produced factors similar to the standard Precontemplation and Action scales, but Contemplation was divided into two factors, "Need for Help," and "Readiness." The Cartoon measure of Stage of Change produced four reliable scales corresponding with four stages. Except for Contemplation, these scales were moderately positively correlated with corresponding URICA scales. The Contemplation scale of the Cartoon measure appears to measure a different dimension of Contemplation than those measured by the URICA. Perceptions of the pros and cons of drug use are adequately measured in this population using a 12-item questionnaire with two six item scales (pros and cons). Test-retest and stability coefficients for all measures were in an acceptable range.

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EVALUATION OF A CARTOON INSTRUMENT ASSESSING STAGES OF CHANGE

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Administering written questionnaires to a street based population can prove problematic for several reasons. Poor language skills can make understanding questions difficult. Cognitive deficits of varying degrees can affect performance on written questionnaires, and for many subjects the sheer boredom of filling out numerous instruments can affect response. Facing these problems with our population in a study assessing the reliability and validity of stage of change measures with stimulant users, we have developed a set of cartoons designed to assess a subject's stage of change. Subjects are given a set of 12 cartoons. There are three cartoons for each stage: Precontemplation, Contemplation, Action, and Maintenance. Subjects sort cards into "Like me" and "Not like me" categories. Initial data have been collected from 160 subjects. We found that factor analysis of this instrument yielded four scales (Precontemplation, Contemplation, Action, and Maintenance) that had good reliability. A cartoon readiness score was significantly and moderately correlated with a URICA readiness score. To examine whether there are any subgroups for whom the cartoon is not a valid measure of the stage of change, we assigned subjects to categories based on their quartile readiness scores on the URICA and cartoons. Fifty-nine subjects (38.8%) had cartoon and URICA readiness scores in the same quartile, while 93 (61.2%) did not. No significant differences were noted between subjects in these two groups in demographic variables or scores from the Picture Arrangement subtest of the WAIS-R, the Symbol Digit Test, or the Trail Making Test Part B.

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PRE- AND IN-TREATMENT PREDICTORS OF RETENTION IN METHADONE TREATMENT USING SURVIVAL ANALYSIS

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This study uses survival analysis to (1) estimate how long the average patient remains in treatment, (2) examine the effects of pre- and in-treatment variables on patient retention, and (3) assess differences in treatment retention among fifteen clinics in the study. A sample of 915 admissions to 15 methadone clinics in New York City in 1989/90 were followed up retrospectively for three years. The sample was 60% male, 48% Hispanic, 28% White, 24% Black; mean age was 35. Time in treatment for up to three years was used as the dependent variable in survival analysis. The estimated average treatment duration was 27 months for patients. The results of Cox proportionate hazards modeling show that 3 of 16 pre-treatment, an 15 of 6 in-treatment variables had significant effects on retention; and that 5 of 15 clinics had significantly lower retention than the median clinic. Being a male patient, separated/divorced, more heroin/cocaine use during treatment, more patient problems per unit time, and greater number of counselors assigned to patients increased the likelihood of leaving treatment; conversely, having mental health problem at intake, more patient strengths (*e.g.,* motivation for treatment, social support), and more staff response to patient problems reduced the likelihood of leaving treatment. This analysis strongly suggests that in-treatment factors are critical to patient retention in methadone treatment, and recommends the use of survival analysis to deal with the "censoring dilemma" inherent in treatment retention studies. **ACKNOWLEDGEMENTS:** Supported by NIDA grant DA-08761

EARLY TREATMENT RESPONSE AND STAGE OF CHANGE IN PRIMARY OPIOID ADDICTS

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Investigated "stage of change" profiles in 102 primary opioid users in a research-based 180-day methadone program which randomized participants into treatment with or without contingency contracting for abstinence from substance use. This report focused on three issues: Do stage profiles shift in response to treatment? Are stage shifts related to the use of contingency contracting in treatment? If stage shifts occur, when are they likely to occur? Subjects averaged 40.5 years of age and were primarily White (39%) and African American (34%), male (71%), unemployed (74%), and single (40%). Fifty-on: subjects received treatment with contingency contracting and 51 received treatment without contingency contracting. Stage of change for opioid use was assessed at intake and then monthly thereafter for six months. Eased on University of Rhode Island Change Assessment (URICA) scores, 4 stage cluster-analytic profiles emerged at intake: Precontemplation (PC) (n=18), Uninvolved (U) (n=42), Contemplation (C) (n=23), and Participation (PA) (n=19). Stewart's test suggested significant stage shifting from Intake to Month One ($p<.0001$) and no significant change thereafter between consecutive months. Stage shifting did not differ between subjects in the two treatment conditions. Note: Of the 33 subjects entering the PA stage at any time, only 3 did so after two months of treatment. We conclude that URICA profiles shift in response to treatment in clinically significant ways. In the context of 180-day methadone treatment, shifts in stage profiles are most likely in the first month of treatment. Multiple assessments of stage profiles over the course of treatment may be useful for understanding response to treatment and tailoring interventions based on this response. Stage assessments later in treatment may be better estimates of post-treatment outcomes than intake stage.

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MODELING TREATMENT RESPONSE: A CROSS-VALIDATED CLUSTER-ANALYTIC TECHNIQUE

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The analysis of treatment effectiveness requires accurate techniques for measuring and describing treatment response. The present study examines the validity of an empirical approach to identifying natural classes of response to treatment over time. These classes, or "treatment response profiles," are identified by cluster analyzing a repeated measure of patient performance collected at intervals during treatment. The procedure is demonstrated in Study 1, using monthly urinalysis results of 103 patients entering methadone maintenance treatment as the performance measure. ASI, mood, and drug use variables found to correspond with the treatment response profiles are then used to construct a logistic regression model of the predictors of treatment response. Study 2, cross-validates the procedures on an independent sample of 66 methadone maintenance patients. Treatment response profiles are found to have good external, and face validity. In addition, they facilitate the analysis of factors predicting treatment response, and of studies comparing the effectiveness of different interventions. Treatment response profiles have advantages over many common measures of treatment outcome, such as performance at follow up, change in performance from treatment entry to follow up, or performance summed across treatment. Since individuals with similar *patterns* of change are combined, not just those whose outcomes or change from baseline are similar, some arbitrariness in the categorization of treatment success and failure is eliminated. By accurately distinguishing patients' treatment responses, this method offers the promise of aiding in 1) the detection of treatment effects, 2) determining optimal patient-treatment matches, and 3) specifying predictors of treatment outcome.

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AN EXAMINATION OF VOCATIONAL BEHAVIORS IN THE CONTEXT OF 12-STEP ORIENTED SUBSTANCE ABUSE TREATMENT

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Most studies on vocational behaviors in drug treatment have been conducted on participants in methadone programs. In contrast, this prospective study examined vocational behaviors among 80 unemployed crack users who enrolled in a 120 day, 12-step oriented, residential treatment program (RTP). The study had two general aims, which were to examine: (a) if participant characteristics assessed at intake predicted job acquisition at a 30 day follow-up; and (b) if job acquisition, vocational skill, and employment in the year prior to treatment predicted psychological functioning (*i.e.,* control, depression) and recovery motivation (*i.e.,* having a sponsor, use of prayer, RTP completion). Results indicated that jobs were more likely to be acquired by persons who: (a) were Caucasian as opposed to African-American; (b) abused multiple substances as opposed to crack only; (c) had a sponsor at intake; and (d) had a vocational skill. Further, job acquisition was tied positively to psychological functioning and having a sponsor, but negatively to the use of prayer, at follow-up. Finally, employment in the year prior to treatment was positively related to RTP completion.

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VOCATIONAL PROBLEM-SOLVING SKILLS TRAINING FOR UNEMPLOYED METHADONE CLIENTS: PRELIMINARY DATA

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This study reports preliminary outcome data for a small-group, psychoeducational, cognitive problem-solving intervention *(Solving Vocational Problems)* designed to increase employment for unemployed methadone maintenance clients. Previous research had indicated that participation in this intervention increased rates of working for unemployed methadone clients at six months post-intervention but not beyond. One hundred nine unemployed subjects (64 male, 45 female) volunteered to participate, gave informed consent, and completed the intake measures. For this preliminary analysis, only subjects who bad completed at least. one face-to-face follow-up with the research assistant (as opposed to mail or telephone follow-up) were included in order to increase confidence in the accuracy of the work data. The subjects meeting this criterion numbered 58 (29 male, 29 female). Mean age was 38.8 years (range = 26-55); mean education was 11.8 years (range = 8-16). Ethnic composition was 50% black, 40% white, 9% hispanic, and 1% Native American.

Although these results must be viewed as preliminary, at this point the data are contrary to expectations, indicating that subjects assigned to the intervention did not find or retain employment at greater rates than controls. In fact, at this point in time control subjects worked significantly more (44.7% of possible weeks) than experimental subjects (15.5%; p = .004). At this point no relationship is apparent between number of group sessions attended and number of weeks worked -- there appears to be no "dose-response" effect. Many participants clearly needed substantial additional treatment, skills, and support services. There were, however, some notable individual successes for some subjects who received the intervention. For these subjects, the group seemed to be a pivotal experience that enabled them to successfully obtain and maintain work. When the data set is more complete and additional follow-ups available for more subjects at more points in time, the characteristics of those who did particularly well or poorly can be examined and analyzed.

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THE EFFECT OF CLINIC CHARACTERISTICS ON PARTICIPATION IN AND OUTCOME OF EMPLOYMENT-RELATED TRAINING

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Three pre-employment interventions are under evaluation in terms of efficacy in helping unemployed or underemployed methadone maintenance patients to obtain and keep employment as part of their rehabilitation. The interventions are Vocational Problem Solving (VPS), based on interpersonal cognitive problem-solving theory; Job Seekers' Workshop(JSW), using behavioral principles and video-feedback; and a combined VPS and JSW. Patients were recruited at three methadone clinics, provided baseline interviews, participated in assigned trainings, and provided 6-month follow-up interviews. Among 107 subjects who have completed follow-up interviews, 70.9% had the same employment status at follow-up as at baseline (55.1% unemployed, 15.8% part employed). 43.9% of study subjects obtained a job post-intervention. More subjects held jobs temporarily between intervention and follow-up than at follow-up. Most jobs paid "under the table". Rates of job-holding post-intervention among subjects unemployed at baseline were: 43.3% for Clinic 1, 20.8% for Clinic 2, and 30.3% for Clinic 3. By intervention, the rates of job-holding were 35.1% for VPS, 36.4% for JSW, and 15.8% for VPS & JSW. Intervention Attenders obtained more jobs than Non-Attenders post JSW (26.4% vs. 12.9%) and post VPS (25.0% vs. 22.2%) but fewer post VPS & JSW (04.2% vs. 08.7). Poor attendance and outcome specifically for combined VPS & JSW was concentrated at Clinic 3. ACKNOWLEDGEMENT: This project was supported by NIDA grant RO1 DAO 8783.

THE RELATIONSHIP BETWEEN PATIENT CHARACTERISTICS AND PARTICIPATION IN AN EMPLOYMENT-RELATED TRAINING PROGRAM

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Substance abusers are often unmotivated to attend treatment despite its desirability or quality. Dam on participation in the Job Seekers' Workshop and Vocational Problem Solving programs with methadone maintenance patients bore this out. Other characteristics may be more powerful. Demographic, psychiatric, psychosocial, and treatment variables were tested for their relationship to training start/completion. Univariate analyses show that significantly related to starting were: less lifetime opiate use (t=-2.01,p=.046), spending less on drugs (t=-2.12, p=.037), lower ASI drug use composites (t=-3.10, p=.002), fewer family/social problems (t=-2.62, p=.010), and fewer problems concentrating (χ^2=4.176,p=.041). Other variables also positively related to attendance included being non-Christian, having lower illegal income, having fewer perceived drug problems, having a history of fewer hallucinations or anxiety and of less sedative and speedball use. A logistic regression found two variables (ASI drug composite and problems concentrating) correctly categorized 70.33% of attenders, but only 53.09% of non-attenders. A second set of analyses looked at completing training once begun. Significantly related were higher lifetime heroin (t=2.02, p=.047) and methadone (t=2.38, p=.020) use, being older (t=2.28, p=.025), higher monthly cocaine use (t=2.16, p=.034), and higher ASI drug composite (t=2.19, p=.031). In a logistic regression none remained, possibly due to a 76.3% completion rate for those who begin, These results are promising, but still do not adequately address the issue of motivation for this population.
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PSYCHOSOCIAL OUTCOMES OF DRUG ABUSE TREATMENT AMONG CLIENTS ENTERING FOUR TREATMENT MODALITIES

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Even though there have been significant increases in the use, abuse, and dependence on cocaine, particularly crack, throughout the 1980s to the present, very little information has been available about outcomes from large-scale multisite studies of treated cocaine users. Drug treatment programs help to produce positive behavior changes in many areas of their clients' lives in concert with reductions in substance use. Changes in areas of psychological functioning, employment, education, and illegal activity are important in determining the overall effectiveness of treatment. In 1989, the National Institute on Drug Abuse (NIDA) initiated the Drug Abuse Treatment Outcome Study (DATOS) to study treatment in typical and stable community programs and to determine treatment outcomes (NIDA Contract No. 271-89-8233).

Subjects for this research sample included 1,352 cocaine-dependent admissions who were regular users in the year before treatment and who completed a l-year posttreatment follow-up interview after being treated in one of 76 different programs in 11 cities throughout the United States in four major treatment modalities.

Comparisons of key behavioral indicators in the year before and the year after treatment were made, and results showed substantial decreases in negative behaviors and increases in positive posttreatment behaviors. There was a 51% decline in suicidal thoughts or attempts, a 69% decline in illegal activities, and a 77% increase in employment from the year before to the year after treatment. Logistic regression explanatory models show that time in treatment had differential effects on outcome behaviors by modality. Various combinations of time in the index treatment episode, and treatment that occurred in the follow-up year, produced positive psychosocial outcomes.

PSYCHOMETRIC DATA ON THE PSYCHOSOCIAL HISTORY

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The Psychosocial History (PSH) is a 2-hour, 300-item comprehensive multidisciplinary interview designed to assess the status, history, and needs of women entering substance abuse treatment programs. It was designed to retain the fundamental structure of the Addiction Severity Index (ASI), while adding supplemental questions considered clinically useful and potentially relevant for predicting outcomes among women. This study examined inter-observer and test-retest reliabilities, and the internal consistency of PSI-I and ASI Composite Scores. It also investigated concurrent validity of PSH and ASI Composite Scores with the SCL-90-R and concurrent and predictive validity with Urinalysis. The Composite Scores of the PSH and the ASI obtained by two trained interviewers (n=13) yielded high inter-observer (r >.90) and satisfactory test-retest reliabilities for PSH and ASI interviews (n=25) with significant correlations for four of six Composite Scores (r =.55 -.70, p <.01). Higher PSH scores for alcohol use and medical status may have been a function of the comprehensive nature of PSH items that prompts women to report their needs in greater depth. Validity analyses showed similar means on four of six of PSI-I and ASI Composite Scores (n=38), significant correlations of PSH (r= .60, p <.01) and ASI (r=.58, p <.01) Psychiatric scores with SCL-90-R Totals, and higher drug use according to PSH and ASI self-reports than urine drug screens. Baseline PSH and ASI Drug and Alcohol Composite Scores were differentiated by drug use patterns measured by urinalysis up to six months in treatment (p <.05). The results show that the PSH is a reliable and valid instrument that may enhance assessment of the status and needs of substance abusing women and warrants further analysis with a larger sample.

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WOMEN-ONLY ALCOHOL AND DRUG TREATMENT PROGRAMS: PROGRAM CHARACTERISTICS AND TREATMENT OUTCOMES

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Alcohol and drug treatment programs designed specifically for women have recently been developed in response to criticism that mixed-sex programs do not adequately address women's specific needs. A secondary analysis of data from the 1991 National Drug and Alcoholism Treatment Unit Survey (NDATUS) demonstrated that women-only programs constituted approximately 15% of residential treatment programs and less than 5% of outpatient programs. Women-only programs across modalities were more likely to be private, non-profit and to utilize a waiting list. Mixed-sex programs were more likely to be private, for-profit; to accept private health insurance; and to accept Medicaid. Mixed-sex programs were more likely to report professionals on staff. Women-only programs were more likely than mixed-sex programs to offer transportation assistance, child care, and self-help groups and to provide special services for pregnant women and cocaine users. Analyses of cumulative data (1987-1994) from the California Alcohol and Drug Data System (CADDS) demonstrated that women in women-only residential programs in Los Angeles were more likely to complete treatment than women in mixed-sex residential programs, while women in mixed-sex outpatient programs had higher rates of completion than women in women-only outpatient programs. These findings suggest that women-only programs differ in funding, types of services, and staffing and that women-only residential programs may enhance the likelihood of treatment completion for women compared with mixed-sex programs.

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MATCHING CLIENTS' NEEDS WITH SERVICES

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This paper reports preliminary results of a study conducted to investigate whether matching treatment services to client needs improves client treatment outcomes. One-hundred and five treatment-seeking drug users were assessed at a treatment referral center on multiple problem areas (alcohol, drug, medical, psychological, family/social, legal, employment, housing) and on other areas of special needs or preferences (transportation, child care, language). A six-month follow-up interview reassessed clients' problems/needs in all areas and collected information on the services received. The results showed that some services significantly improved client outcome for those who expressed needs for those services. Notably, transportation, child care, vocational services, and housing services showed positive impacts. However, further examination suggested that some clients with severe problems had not fully acknowledged their needs, indicating that additional sources for determining needs may be important. Finally, some services (*e.g.,* legal), although provided by the program, might have been insufficient to adequately resolve the needs of the clients.

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CORRESPONDENCE OF DRUG TREATMENT PROGRAM SERVICES DESIRED, RECEIVED, AND OFFERED

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This poster reports on the services offered by 294 drug treatment programs surveyed in Los Angeles County, California, and the services desired and received by 203 treatment-seekers in that system. In an assessment interview subjects were asked which services they thought would be important ("desired") to have as part of their drug treatment. Of 203 subjects who have been followed-up so far, 109 (54%) went to treatment programs that had responded to the survey. Altogether, 24 different programs were utilized for which services information was available. Analyses were conducted to compare program services offered with program services desired in the system as a whole and services offered, desired, and received in three outpatient drug-free programs attended by 91 of the subjects. There was some correspondence between services most frequently desired and services most frequently offered, and between services least frequently desired and least frequently offered in the system as a whole. The correspondences among services offered, desired, and received in three similar outpatient drug-free programs were quite varied with only individual and group counseling being desired and received by more than 70% of the clients in all three programs. There was generally larger variation in the percent of time *services received* matched *services desired* for all other services asked about. Further investigation of this type may enhance the process of providing referrals to drug treatment.

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PATIENT-TREATMENT MATCHING IN COCAINE ABUSE TREATMENT

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This study evaluated the efficacy of two outpatient psychotherapies, a cognitive-behavioral group and a 12-step facilitation group, in treating cocaine abuse. Subjects (N=128) were randomly assigned to treatment conditions, and assessed at baseline and weeks 4, 8, 12, and 26 on biologically-verified cocaine abstinence and a battery of psychometric measures. Both treatment conditions were standardized using detailed treatment manuals and offered 36 group therapy sessions over a 12 week period. We hypothesized that subjects treated with cognitive-behavioral treatment would be significantly more likely to achieve abstinence than subject treated with 12-step facilitation. We also proposed a series of matching hypotheses, suggesting that: (a) 12-step facilitation would be differentially effective for patients who evidenced high levels of religious beliefs or 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, or who had a history of Major Depression. All of the subjects were crack cocaine smokers; most were male (99%), African-American (80%) unemployed (84%) and homeless or marginally housed (75%). When outcome was examined across undifferentiated groups of cocaine abusers, subjects in the cognitive-behavioral condition were significantly more likely to achieve abstinence than subjects in the 12-step condition. Three of the five matching hypotheses were also supported, suggesting that both 12-step facilitation and cognitive-behavioral treatment may be differentially effective for identified subgroups of cocaine abusers.

EXPLAINING VIGILANT PARTICIPATION IN DRUG AND ALCOHOL TREATMENT PROGRAMS

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Recent research indicates that vigilant, or frequent, participation in counseling related to drug and alcohol treatment is strongly associated with positive treatment outcomes, although the underlying causes of vigilant participation are not well understood. One goal of a four-year, longitudinal study of 330 treatment participants funded by the Center for Substance Abuse Treatment was to determine the causes of vigilant participation in Los Angeles metropolitan outpatient programs. The findings indicate that both program and client characteristics are associated with vigilant participation. Transportation, financial, and other barriers had some effect on the frequency of treatment participation, but the most salient program characteristic was the availability of counseling. Making counseling more available by reducing counselor caseloads dramatically (and immediately) increases the frequency of client participation. Although women were more likely than men to participation in counseling, cognitive factors are the strongest individual-level predictors of vigilant participation. Important cognitive factors include: (1) A strong motivation to end a drug and alcohol using lifestyle, (2) a perception that the treatment program is useful in affecting the desired change, and (3) an acknowledgment of a high probability, or risk, of relapse. The research and policy implications of these findings are discussed.

CORRELATES OF TREATMENT UTILIZATION IN A SUBSTANCE ABUSING SAMPLE

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As part of a study on treatment utilization and effectiveness, over 5,000 subjects were surveyed at selected jails, hospital emergency rooms, and sexually transmitted disease clinics in Los Angeles County. Information collected at this interview included drug use and treatment history, HIV risks, and legal problems. A urine sample was collected to validate self report of recent drug use. A group of subjects who admitted use of illicit drugs in the year prior to the interview were randomly selected for one-year follow-up interviews, which included additional questions about help-seeking, criminal involvement, medical care, and psychological problems. As of May, 1996, 717 one-year follow-up interviews had been conducted. One hundred and twenty-seven subjects (17.7%) claimed to have used heroin regularly for over one year. Four hundred and sixty four (64.7%) used cocaine (in powder or crack form) regularly for over a year. Eighty-eight (69.3%) of the regular heroin users and 248 (53.4%) of the regular cocaine users had been in treatment at least once (mean times 2.6 and 3.5, respectively). Analyses, including logistic regression, were conducted in order to determine correlates of treatment utilization by regular users of heroin and cocaine. For cocaine users, women were significantly more likely than men to have been in treatment, while Latinos were significantly less likely to have treatment experience than whites. Years of cocaine use and experiencing an overdose were also significantly related to treatment utilization. For heroin, again, female users were more likely than males to have utilized treatment. Overdose was also significantly related to treatment utilization. Number of incarcerations and having children were negatively related to treatment utilization.

TRACING A NATIONAL SAMPLE TWO DECADES LATER

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A long-term follow-up of a national sample requires different tracing considerations from those needed for a short-term or a local population follow-up. Field and telephone tracing can become financially infeasible when respondents reside in geographically-spread areas. When respondents have not been contacted for a prolonged duration of time, traditional “forward’ tracing based on the last contact may not be efficient. In the feasibility and field entry phases of the Washington University Vietnam Era Study (VES), over 1,200 Vietnam veterans and a comparison group of civilians, last contacted in 1974, were traced. The respondents are all male and now average 45 years old; about half of veterans were originally recruited based on a list positives for drug use urinalysis at their departure from Vietnam. Tracing sources included health search sources, VA records, commercial services such as Trans Union, PhoneDisc and Internet sources. Tracing proceeded with more labor-intensive methods and confirmation calls. Of the follow-up eligible sample of 1,189 as of June 1994, 93.4% were identified as dead or located with addresses through electronic tracing or direct contact if unlocated; 83.1% of surviving respondents met our single exact matching criteria for electronic tracing. Tracing data also provided outcomes unobtainable by interviews. Such data helped anticipate areas of difficulty in the fieldwork and assessing interview outcomes early in the study. Tracing updates during the first half of 1996 yielded more information than was previously available, reflecting the rapid expansion of information networks since 1994. On the other hand, unique identifiers such as the social security number are critical for efficient tracing. The tracing results were maximized by combining several sources; no one method should be considered adequate. Case-by-case detective work is required in the later stage tracing. A certain segment of the population does not leave much of a paper trail even today. The population at high risk for continuous substance abuse remains hard to find even in the information age. ACKNOWLEDGEMENTS: Supported in part by NIDA grant K02-DA00221,R01-DA09281 and R01-DA07939

THE PREVALENCE OF SUBSTANCE USE DISORDERS IN GENERAL HOSPITAL INPATIENTS OF AGES 18 TO 49

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Previous studies have suggested that substance use disorders (SUD's) are prevalent in inpatients of general hospitals. These studies were limited in the validity of their measures of SUD's, their failure to distinguish between current and lifetime disorders, or their lack of attention to drugs other than alcohol. The current study used validated diagnostic interviews to assess for current and lifetime alcohol and other drug abuse and dependence, excluding tobacco, among patients of ages 18 through 49. Patients were recruited from the general medical, general surgery, and orthopedics services of University Hospital in Madison, Wisconsin. The sample included 363 patients, or 86.4% of those recruited. The participants and non-participants were demographically similar. Nearly half the subjects (49.6%) had lifetime SUD's. Over one -fifth (21.8%) had current SUD's, and 11.8% were currently dependent on at least one substance. The current prevalence of SUD's was 29.2% in males, and 10.0% in females. Age, race, marital status, and insurance status were associated with some patterns of substance use but not with overall prevalence. 16.3% of the subjects had alcohol disorders only; 2.5%, other drug disorders only; and 3.0%, both; thus, approximately one-fourth (25.2%) of the subjects with SUD's had current drug abuse or dependence. The prevalence of current disorders involving marijuana was 2.8%; opioids including heroin, 2.5%; cocaine, 1.9%; sedatives and tranquilizers, 0.6%; stimulants, 0.3%; and inhalants, 0.3%. The prevalence of current drug disorders is likely to be higher in hospitals that serve localities where drug use is more prevalent than in Madison. Hospitals are fertile ground for identification and intervention programs. For such programs, brief screening protocols that focus on alcohol and other drugs are needed.

APPLYING NEURAL NETWORK MODELS TO EPIDEMIOLOGY

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Epidemiologic measures are inherently imprecise in predicting outcomes of interest. A large number of variables are ofter needed to explain a relatively small amount of variance in the data. Standard statistical techniques currently available in epidemiology and social sciences frequently are ill-suited to deal with skewed distributions, non-linear associations and complex structures. We present pilot data comparing the performance of the neural-network (NN) models and genetic algorithms (GA) to conventional statistical techniques. The NN model, with its origin in artificial intelligence, is thought to yield better prediction for a variety of outcomes because of its training ability, by utilizing the information in the data itself, and of flexibility for fitting functions. GA is an efficient optimization technique which allows flexible fitting functions and can be employed for selecting best predictive variables. Two sets of analyses were carried out using two datasets: 1) childhood and adult antisocial behaviors were used to "mimic" the diagnosis of antisocial personality disorder, using general-population and institutional samples (N= 3,500) from the St. Louis antisocial personality disorder, using general-population and institutional samples (N= 3,500) from the St. Louis Epidemiological Catchment Area (ECA) project; and 2) time-specific substance abuse and combat, and predisposing measures were used to predict mortality over two decades among Vietnam-theater general and drug-positive veteran and nonveteran comparison samples from the Washington University Vietnam Era Study (VES, N=1,227). The Receiver Operating Characteristics (ROC) methodology was used to evaluate NN and GA's performance in comparison to standard techniques. Results show NN performed slightly to substantially better than conventional statistics. NN improved an ROC measure by as much as 14%. Variable selection using NN and GA yielded a set of best predictors substantially different from those chosen by logistic regressions. NN and GA applications in epidemiology are feasible and can aid conventional statistical analysis to improve epidemiologic prediction. ACKNOWLEDGEMENTS: Supported in part by NIDA grants K02-DA00221, R01-DA0928 1 and R01-DA07939.

CORRELATES OF ANNUAL BUDGET OF DRUG TREATMENT PROGRAMS: A PRELIMINARY EXPLORATION

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This is a secondary analysis that explores the factors that may be related to the amount of annual budgetary moneys received by drug treatment programs in Los Angeles County, California. Data for this project were collected using the Treatment Referral Network Survey (Hser & Polinsky, 1994). Data from this survey were completed by treatment staff. These data were extracted from 294 programs, covering six treatment modalities: (1) hospital inpatient; (2) residential; 3) outpatient drug-free; (4) outpatient methadone maintenance; (5) outpatient detoxification with medication; and (6) day treatment. Probit analysis, with dummy codes for treatment modality and outpatient methadone maintenance as the comparison group, was performed to test for group (modality) differences in annual budget. Results indicate that significant predictors of annual budget are: (1) treatment modality ($p=.0001$); (2) total client capacity ($p=.0001$); (3) number of medical services ($p=.0001$); (4) number of case management services ($p=.0001$); (5) academic educational services ($p=.0023$); (6) number of vocational services ($p=.0250$); and (7) average duration of treatment ($p=.0272$). Findings suggest: (1) funding mechanisms vary across treatment modality, and (2) treatment staff may use information about their own program to better understand which factors may be considered "influential" by funding agencies in their funding decisions.

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LOFEXIDINE SUPPRESSES WITHDRAWAL IN MORPHINE-DEPENDENT RHESUS MONKEYS

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Clonidine (Clon), an α_2-noradrenergic agonist, has been shown to partially suppress withdrawal in opiate-dependent humans (Washton and Resnick, 1981) but, not without undesirable side effects such as drowsiness and dizziness. Clon has been studied in our laboratory (Aceto and Harris 1981) and was found to attenuate withdrawal in monkeys maximally dependent on morphine. However, prominent side effects were noted.
Based on this observation, lofexidine (Lof), a structural analog of Clon, with purported fewer side effects (Maner *et al,* 1980), was administered to morphine-abstinent monkeys at doses of 0.025 and 0.1 mg/kg. A dose-related reduction in withdrawal signs was noted. At these doses fewer side effects such as drowsiness were observed. Lof may be more efficacious than Clon in the treatment of opiate abuse.

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SPINAL MUSCARINIC RECEPTOR SUBTYPE MEDIATION THE PROCESSES OF MORPHINE DEPENDENCE AND TOLERANCE IN RAT

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Preliminary studies in this laboratory have demonstrated that naloxone-precipitated withdrawal symptoms are blocked and morphine tolerance is reversed by *systemic administration of muscarinic receptor* antagonists of MI and M2 receptors. The present study was initiated to determine whether the selective muscarinic receptor antagonists by intrathecal injection are capable of inhibiting the morphine withdrawal symptoms and morphine tolerance. Catheterization of the spinal subarachinoid space was performed by inserting a length of PEIO tubing, terminating in the TII-TI2 segments of the spinal cord. Male Sprague Dawley rats (n=7,in each group) were made morphine dependent after recovery from the surgical procedure. Pretreatment with pirenzepine (i.t.), a selective MI receptor antagonist, at doses *of* 5 μg/kg, 20 μg/kg and 100 μg/kg, the total ratings of naloxone(4 mg/kg) precipitated withdrawal signs across the session were 27±-2.0, 19±-3.6, 13±-2.5 respectively, which were different significantly from that of placebo(34±-3.7). Methoctramine (i.t.). a M2 *receptor antagonist, only* at *dose* of 200μg/kg could inhibit the withdrawal symptoms. Additionally, concurrent with pirenzepine (i.t.) for six days significantly attenuated the development of morphine tolerance produced by twice daily injection of morphine (10 mg/kg s.c.). This attenuation of morphine tolerance by pirenzepine was dose-dependent. Methoctramime (i.t.) also could attenuate the morphine tolerance, but no. in the dose-related manner. These observations showed that muscarinic receptor subtype predominantly MI within the spinal cord mediated the *processes* of morphine dependence and tolerance in the rat.

SELECTIVE BLOCKADE OF MORPHINE-INDUCED TOLERANCE AND ABSTINENCE BY NALTRINDOLE

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Delta (∂) opiate receptors may contribute to the development of tolerance to morphine-induced antinociception. The goal of the present study was to determine the extent of ∂ receptor involvement in morphine-induced tolerance and dependence. Rats were treated chronically with morphine and the ability of the selective ∂ antagonist, naltrindole to prevent the development of tolerance and signs of morphine abstinence determined. After morphine pellet implantation or chronic morphine injection, tolerance developed rapidly to morphine-induced antinociceptive, morphine-stimulated ACTH release and morphine-induced respiratory depression. Daily treatment with naltrindole (10 μg, icv) for 2 days blocked the development of tolerance to morphine-induced antinociception. However, naltrindole treatment failed to block the development of tolerance to morphine-stimulated ACTH release or morphine-induced respiratory depression. When abstinence was precipitated with naloxone, a robust withdrawal occurred. Naltrindole significantly attenuated the incidences of wet dog shakes, forepaw treading, salivation as well as the percentage of rats exhibiting rhinorrhea, diarrhea and vocalization on touch. The only withdrawal symptom unaffected by naltrindole was ptosis. In conclusion, naltrindole selectively blocks the development of tolerance to morphine. Moreover, the ability of naltrindole to block tolerance to morphine-induced antinociception but not morphine-induced respiratory depression may be beneficial when morphine is used clinically for the management of chronic pain.

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CODEINE: A COMPARISON OF DEPENDENT AND NON-DEPENDENT REGULAR USERS

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Codeine is a commonly used analgesic. We characterized regular (at least 3 days/wk for six months, excluding cancer patients) codeine users through a self-completed 27 page questionnaire (n=339, 49% male). These subjects were using codeine at least 5-6 days/week (70%) for an average of 12±9 years. Codeine-acetaminophen products were most commonly used (total 70%, 30 mg 37%, 8 mg 23%). While 30% of subjects self-identified problem codeine use, 37% met DSM-IV criteria for codeine dependence (32% of whom did not consider their codeine use a problem). The most commonly endorsed DSM-IV criteria were tolerance (85%), using more or for longer than intended (81%) withdrawal (82%) and difficulty stopping (78%). Dependent subjects were younger (mean 40 vs 47 years, $p<0.001$), used higher doses of codeine (mean, 179 vs 74 mg/day, $p<0.001$), and were more likely to obtain codeine from friends, family, or the street (61% vs 12%) compared to non-dependent subjects. They also identified specific problems related to their codeine use eg. depression (23% vs 4%), anxiety (21% vs 4%), GI problems (13% vs 4%), and other drug use problems (alcohol 57% vs 26%, cannabis 23% vs 5%, sedative/hypnotics 33% vs 12%, oxycodone 24% vs 2%, heroin 11% vs 2%). Most were taking codeine for chronic pain (80%), although dependent subjects currently found codeine less effective than nondependent subjects. Regular codeine use is associated with high rates of dependence. Better recognition of the consequences of such use is needed. ACKNOWLEDGEMENTS: Supported in part by a NIDA Grant DA06889.

CHRONIC TREATMENT WITH A CONTROLLED-RELEASE OPIOID: REDUCTION IN SPECIFIC DRUG EFFECTS OVER TIME

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A Modified Specific Drug Effect Questionnaire (MSDEQ) was utilized as part of a pharmacodynamic assessment tool in patients with moderate to severe chronic pain secondary to documented osteoarthritis (N=106) who were enrolled in an open-label treatment protocol with a new controlled-release oxycodone (OxyContin™ Tablets). Patients enrolled were judged to be candidates for chronic opioid treatment. Treatment was instituted at 10mg q12h and titration allowed as needed. Standard efficacy and safety data were collected on these patients. At weeks eight and 40, the patients reported to the clinic before taking their morning dose. They were asked to complete ten assessments identified in the MSDEQ (see table; Feel Drug Effect, Itchy, Relaxed, Sleepy, Drunk, Nervous, Full of Energy, Need to Talk, Sick, Dizzy). The responses were measured on a horizontal 100mm VAS (0-not at all, 100-an awful lot). The results shown below present the mean VAS score at weeks eight and 40 and the percent change over this interval. Pain intensity was moderate-severe at baseline and mild-moderate at weeks eight and 40.

MEAN MSDEQ VAS SCORES (mm)

	D.Eff	Itch	Rel	Slep	Dru	Ner	FoE	Talk	Sick	Dz
week 8	20.4	10.4	41	23.6	3.8	15	23.4	11.5	8.5	5.9
week 40	14.6	8.3	28.9	13.1	2.5	10.8	17	9.4	3.3	5.5
reduction	28%	20%	30%	44%	34%	28%	27%	18%	61%	7%

The mean daily oxycodone dose for week eight and week 40 was 39mg and 45mg respectively. The results show that absolute values for the items after eight weeks are generally small and that there is a continued reduction in these reported effects over time. The data further show that this reduction occurs with stable dosing and stable pain control. We conclude that continual dosing with opioids results in reduction in opioid-related effects without an escalation in dose or reduction in pain control.

COLD WATER IMMERSION MODULATES THE REINFORCING EFFECTS OF FENTANYL IN VOLUNTEERS

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Stress (*e.g.,* pain) has been shown to modulate the reinforcing effects of psychoactive drugs in both infrahumans and humans. The present study was designed to examine whether a painful stimulus, forearm immersion into ice-cold water, modulated the reinforcing and subjective effects of fentanyl, a full mu agonist, in non-drug abusing volunteers. Participants (N=10) in this IRB-approved, crossover double-blind study, and after written informed consent, attended three separate sessions, each session consisting of two sampling trials and three choice trials. During sampling trials subjects administered via patient-controlled analgesia pumps both 50 mcg of fentanyl and saline, and then at hourly intervals could choose between he two pumps (drugs). Five min after each of the five injections in a session, participants had to immerse their forearm for 3 min in either 2, 10, or 37° C water. Fentanyl significantly reduced participants' self-reports of pain in the two and 10° C water conditions. Participants on 77% of choice occasions in the two and 10° C water conditions chose to self-administer fentanyl (significantly different from chance levels as determined by a test of binomial proportions). In contrast, fentanyl choice rate (60%) in the 37° water condition was not different from chance. Several subjective effects of fentanyl were also modulated by the temperature of the water bath: for example, subjects reported feeling "elated" during forearm immersion into 37° C (5 min after injection of fenlanyl), but did not report such an effect during forearm immersion into 2°C or 10° C water. Increased "floating" ratings after fentanyl injections were attenuated during the cold-water immersions. We conclude that the reinforcing effects of the analgesic, fentanyl, in volunteers without a history of opioid abuse, are modulated by a painful stimulus.

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GAMMAHYDROXYBUTYRIC ACID FOR DEXTOXIFICATION

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The quality of opiate detoxification treatment is still unsatisfactory. Detoxification treatment with neuroleptics or alpha-adrenegic drugs could not be well established due to major side effects and inefficacy. The treatment based on a daily reduction with methadone yields to good compliance during the withdrawal treatment due to lacking major side effects but the mean duration of staying on an in-patient basis is more than three weeks. Gammahydroxybutyric acid (GHB) has been demonstrated to suppress ethanol withdrawal symptoms in rats and humans. We investigated ten opiate dependent patients (DSM IV: 304.0) applying GHB orally on an in-patient basis. Drug history was evaluated by Europe Addiction Severity Index (ASI), withdrawal rating scale WANG has been applied frequently. Blood pressure and heart rates have been monitored during detoxification treatment. First, GHB has been applied every four hours (Somsanit R). Intially we administered a dose of 150 mg per kg per day, which showed efficacy, but the successful suppression of withdrawal syndromes lasted only up to two hours after application of GHB. We enhanced the dosage of a maximum of 100 mg per kg per single dosage, changed the scheme and applied it orally every two hours. Using this dosage of GHB no major withdrawal syndromes were noticed during detoxification treatment period. Urine sample was negative for opiates on day 5, no additional medication has been necessary, with exception of oxacepam for the treatment of sleep disturbances. GHB was discontinued on day 8 without reoccurrence of any symptoms, patients were discharged on day 10. GHB appears to be a useful approach for opiate detoxification.

TIME COURSE OF NALOXONE-PRECIPITATED WITHDRAWAL AFTER ACUTE BUPRENORPHINE EXPOSURE IN HUMANS

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Buprenorphine (BUP) is a partial agonist with demonstrated efficacy in the treatment of opioid dependence. BUP maintenance produces physical dependence. There has been little systematic work examining the onset latency or offset time-course of BUP-induced physical dependence. In the present study, antagonist challenges following acute agonist pretreatment were used to explore the development and time course of BUP-induced physical dependence. Six non-dependent opioid-experienced volunteers were treated with varying acute BUP doses (0, 8 or 32 mg s.l.) and then challenged with 3 mg i.m. naloxone 1, 4, 7, and 10 days post-BUP treatment. A fourth condition (32 mg BUP treatment, active naloxone challenge on day 7 only) was included to assess the effects of multiple challenges. Data indicate that naloxone challenges precipitated withdrawal 1, 4, and 7, but not 10 days after single dose BUP treatment, suggesting that physical dependence can be detected after a single dose of BUP and that the physical dependence engendered by BUP has a prolonged post-exposure duration.

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THE EFFECT OF LAMOTRIGINE ON NALOXONE-PRECIPITATED OPIATE WITHDRAWAL

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NMDA antagonists attenuate opiate withdrawal in pre-clinical studies. The anticonvulsant Lamotrigine acts at voltage-activated sodium channels and attenuates glutamate release in vitro. The effect of Lamotrigine pretreatment on precipitated opiate withdrawal was studied in hospitalized heroin-dependent subjects stabilized on levorphanol 6mg po tid. After an acclimatization challenge, three double-blind challenges were done with balanced, randomized pretreatment with placebo, Lamotrigine 250mg, or 500mg. Pretreatment was in equal oral doses 6 and 3 hours before i.v. naloxone 0.4mg/70kg. Opiate withdrawal measures were summarized as AUC-change and analyzed in a one-factor repeated measures ANOVA with planned comparisons of each active Lamotrigine dose to placebo. Six subjects completed all challenges and a seventh did not complete the 250mg Lamotrigine. There were trends ($P<.10$) towards attenuation of systolic blood pressure increases by Lamotrigine, attenuation of coughing and muscle twitching by 500mg Lamotrigine, and attenuation of diastolic blood pressure increases by 250mg Lamotrigine. Lamotrigine alone was well-tolerated in subjects who did not develop a rash from it. Lamotrigine did not demonstrate a large effect to attenuate withdrawal severity, but appeared to attenuate physiological withdrawal signs in some subjects.

ACKNOWLEDGEMENTS:

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REMOTE DRUG TREATMENT INFORMATION SYSTEM IN A TRIAL COMPARING BUPRENORPHINE SUBLINGUAL LIQUID TO TABLETS

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We provide pharmaceutical support for a clinical trial comparing buprenophine sublingual liquid to tablets. The trial requires controlled, double blinded administration of placebo tablet with active liquid or vice versa, with a crossover treatment. In addition dosage levels can be adjusted weekly in a blinded manner according to clinical conditions. We developed Remote Drug Treatment Information System (RDTIS) for this trial to: (1) assure maintenance of blinding throughout the trial, (2) prevent dispensing errors, (3) decrease manual documentation, (4) automate data entry, (5) increase ease of dose adminis ration, and (6) assist clinicians in assessing therapy and adjusting doses. RDTIS uses a computerized relational data base and a bar coding system. Bar codes are placed on each patient's identification card and on each drug dosage. The computer monitors each patient in the study and all dosages available at the study site. When a dose is administered the clinician scans the patient's bar code and the drug dosage bar code. The computer verifies that the dosage is correct for that patient and documents the dose administration. In addition RDTIS includes data bases for patient-completed quality of life assessments and results of urine drug screens. Dosage adjustments can be entered into the system based upon the computerized urine drug screen reports. Data arc downloaded to us at regular intervals. RDTIS helps us to assure data accuracy and completeness in addition to providing automated support to clinicians at the study site.

COMBINING NALTREXONE WITH BUPRENORPHINE FOR OPIOID DETOXIFICATION

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The safety of initiating naltrexone maintenance during a d-day buprenophine taper (4,6,4,2 mg/day) was documented in a previous trial[1]. Two questions remained unanswered: 1) could the intensity of naltrexone - precipitated withdrawal be decreased further by increasing the buprenorphine dose 2) is it safe to administer 50 mg of naltrexone to buprenorphine-placebo patients at the time of discharge, on day 8, of detoxification? In this study the buprenorphine taper was modified (increased) to 12, 8, 4, 2 mg/day. In a randomized double-blind two-group design, naltrexone was administered on days 2-8 in the naltrexone group [BN group], and on day 8 only in the placebo group [BP group]. Subjective and objective measures of opioid withdrawal were recorded at intervals until day 9 or 22 hours after the last naltrexone dose. Sixty opioid-dependent patients (DSM-IV criteria) participated (age 31 ± 0.7 years, African-American 88%, males 52%). Average length of stay (± SE) was 6.0 ± 0.4 days for the BN group, and 7.3 ± 0.4 days in the BP group ($p = 0.01$). Rate of treatment completion was 53% in the BN group and 75% in the BP group (NS). Overall peak of opioid withdrawal occurred on days 2 in the BN group, and on days 6 and 8 in the BP group. The magnitude of naltrexone precipitated withdrawal on day 2 appeared to be lower than in the previous (lower buprenorphine dose) study. Introducing naltrexone on day 8 (4 days after the last buprenorphine dose) precipitated withdrawal equivalent to that seen on day 2. Withdrawal exacerbation on day 2 was more acceptable to patients than on day 8 (clinical observation). Thus, initiating naltrexone maintenance on day 2 of a buprenorphine taper appears to be a better treatment option.

[1]: Umbricht-Schneiter, A.; Montoya, I.D.; Demuth, K.L.; Preston, K.L. Opioid Detoxification with Buprenorphine Alone or in Combination with Naltrexone NIDA Research Monograph 162, 1996, p. 117.

MODERATE VERSUS HIGH DOSE METHADONE IN THE TREATMENT OF OPIOID DEPENDENCE

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This outpatient clinical trial examined the efficacy of moderate (M) versus high (H) dose methadone in the treatment of opioid dependence. Opioid-dependent volunteers (N=192) were randomly assigned to 30 weeks of double-blind methadone dosing at the time of entry to an outpatient treatment/research clinic. There were no significant differences between groups on demographic features. Following initial stabilization on 40 mg (M) or 80 mg (H) of methadone, double-blind dose increases up to 50 mg (M) or 100 mg (H) were possible based upon evidence of continued illicit opioid use as determined from urine testing. Subjects were assigned an individual counselor, and had group therapy and primary medical care services available on-site. Results show the two groups did not differ on treatment retention (mean days in treatment were 157 and 159 for M and H groups, respectively). The H dose group had a significantly lower mean rate of opioid-positive urine samples during treatment (53%) compared to the moderate-dose group (62%) ($p<0.05$), with no significant differences in rates of cocaine or benzodiazepine-positive urine samples. Significant improvements over time were seen for both groups on self-reported drug use and other measures assessed by the Addiction Severity Index (ASI). These results demonstrate that higher methadone doses may significantly decrease rates of illicit opioid use, although substantial amounts of illicit opioid use can persist during treatment for patients treated with doses of 80-100 mg per day of methadone.

ACKNOWLEDGEMENTS:

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PREFERENCE FOR ORAL METHADONE DOSES IN A LABORATORY SETTING

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In an earlier study examining the interacting effects of response requirement and methadone dose, responding maintained by the larger dose was disrupted less by increased work requirement than responding maintained by smaller doses indicating greater reinforcing effects for the larger dose. In this study the relative reinforcing effects of 0.108, 0.054 and 0.027 mg/ml were examined systematically by examining preferences for these doses. Methadone-maintained patients stabilized at a dose of 80 mg of methadone per day were recruited as subjects. A sixty minute self-administration trial was scheduled Tuesdays through Thursdays. During a trial two methadone doses were concurrently available. Completing a response requirement of 100 responses (FR 100), on one button dispensed 10 ml of the first methadone dose. Completing the equivalent response requirement on the second concurrently available response button dispensed 10 ml of the second methadone dose. The methadone dose combinations concurrently available during a session were 0.108 and 0.027 mg/ml, 0.108 and 0.054 mg/ml, and 0.054 and 0.027 mg/ml. Dose combinations were presented in counterbalanced order across subjects. The 0.108 mg/ml dose was preferred to the 0.054 or 0.027 mg/ml doses. The 0.054 dose was not reliably preferred to the 0.027 mg/ml dose. The preference for the 0.108 mg/ml dose relative to the smaller unit doses is consistent with our previous results that demonstrated large unit doses maintain more responding, have greater reinforcing effects, relative to small unit doses.

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MOOD STATE AND PLASMA CONCENTRATIONS IN METHADONE MAINTENANCE.

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One cause of poor treatment compliance in maintenance programs is the failure of methadone to be effective over the entire 24-hour dosage interval. Approximately 35% of methadone maintenance patients in South Australia report opioid withdrawal symptoms in the period prior to each dose. The present study compared patients who experienced such withdrawal symptoms with a group who did not, in order to determine whether the magnitude and temporal pattern of their mood states also differed. Eighteen methadone maintenance patients were admitted to an inpatient unit for a single 24-hour period. The Profile of Mood States (POMS) (McNair et al.1971) was administered on 13 occasions within this period. Measures were also made of withdrawal severity and blood samples were collected to determine methadone plasma concentrations. There were no significant differences between the groups with respect to age, gender, oral methadone dose or other treatment variables. POMS sub-scales showed temporal patterns consistent with changes in methadone plasma concentrations. Mean scores on the Vigour sub-scale peaked approximately 3-4 hours post-dosing and then decreased throughout the rest of the dosage interval. All other sub-scales (Tension, Depression. Anger, Fatigue, Confusion and Total Mood Disturbance) showed an inverse relation, peaking in the period immediately prior to the methadone dose. Patients with higher withdrawal intensity showed overall levels of mood disturbance that were higher, as well as a greater degree of change in mood disturbance and plasma methadone concentrations. These results indicate that the failure of methadone to 'hold' over the full 24-hour period is associated with more pronounced rises and falls in plasma methadone concentrations and mood disturbance.

REFERENCES: Furnished upon request of senior author

LAAM TREATMENT AND PATIENT RETENTION: ANOTHER PERSPECTIVE

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Seventy (70) percent of methadone maintenance patients treated with LAAM return to methadone within six months, according to a report delivered at the 1995 CPDD annual conference. Based on preliminary data collected from participants in a 48 week, NIDA funded feasibility study of take home LAAM, our group notes a different experience.

We evaluated subjects' acceptance of LAAM and their opiate substitution treatment preferences, in 26 persons who had either completed (23) or terminated (3) from the LAAM feasibility study. LAAM was considered more effective than methadone, and was rated better than methadore across most dimensions measured. LAAM was also the overwhelming treatment choice for study completers. Of the 23 subjects who completed all 48 weeks of treatment, 19 (82.6%) opted to continue on LAAM in a fee-for-service setting compared to four (17.4%) who switched to methadone. Further, of those who switched, only two (.8.7%) elected fee-for-service methadone due to preference, while one (4.3%) chose to participate in 21 cocaine-treatment trial for methadone-maintained patients and one (4.3%) cited public funding restrictions as the reason for changing.

These findings appear to establish LAAM as an effective and, in many cases, preferred option to methadone for treatment of opiate dependence.

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TREATMENT PERFORMANCE AND BEHAVIOR CHANGES ASSOCIATED WITH CONTINGENCY MANAGEMENT AND RELAPSE PREVENTION FOR COCAINE DEPENDENCE

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Treatment response and behavior change were assessed in 25 primary cocaine users and 20 cocaine-using methadone patients participating in an ongoing study receiving either contingency management (CM), relapse prevention (RP), both CM and RP, or methadone (MM) only. Measures were the Treatment Effectiveness Scores (TES, total number of stimulant-free urines out of a possible maximum of 48), and the Abstinence Behaviors Survey (ABS, a survey of behaviors associated with cocaine abstinence). Preliminary results indicated a superior response to treatment by CM and CM&RP groups compared to RP. There was a greater amount of behavior change in the RP and CM&RP groups compared to CM; primary cocaine users also reported more behavior change than methadone patients. TES and ABS scores were not correlated. Follow-up data eventually may indicate the relative clinical efficacy of promoting either maximum treatment involvement and performance, behavior change, or both.

RAPID LAAM INDUCTION IN AN OUTPATIENT CLINICAL TRIAL

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Rapid induction onto high dose LAAM may enhance treatment efficacy. This study assessed the clinical efficacy of a LAAM rapid dose induction schedule. One-hundred eighty opioid dependent patients were enrolled into a 29-week outpatient 3-dose comparison study. Patients were stratified and assigned (random, double-blind) to thrice-weekly maintenance dose conditions (Low: 25/25/35; Medium: 50/50/70; and High: 100/100/140 mg). For the first 2 weeks, patients attended the clinic daily and received active medication and placebo on alternate days. Duration of patients' induction period varied by assigned maintenance dose. Patients assigned to the low dose condition (N = 62) received 25 mg on alternate days, patients assigned to the medium dose condition (N = 59) were inducted onto 50 mg in 7 days, and those assigned to the high dose condition (N = 59) were inducted onto 100 mg in 17 days. Induction effectiveness was assessed in the patients (N = 142) who completed the first 5 weeks of treatment. Outcome measures included retention in treatment, urine specimens positive for opioids, and side-effects. There was a trend ($P < .06$) for lower retention in the high dose group. No significant difference was observed in urine specimens positive for opioids. There was a significant group by gender difference with males in the high dose group having fewer urine specimens positive for opioids. Fifty percent of dropouts in the high dose group were due to agonist-like side effects compared to 10% and 0% in the medium and low dose groups, respectively. It is concluded that: 1) a dose induction schedule with increases of 10 mg every-other-day to 50 mg is feasible; 2) during induction there may be a difference in effectiveness based on gender; and 3) a longer dose induction schedule for the high dose group may improve retention in treatment and reduce opiate agonist-like side effects.

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IMPROVEMENT IN NALTREXONE TREATMENT COMPLIANCE WITH CONTINGENCY MANAGEMENT

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Clinical experience has shown that poor compliance with naltrexone treatment seriously compromises its clinical utility. This study tested the efficacy of contingency management for improving compliance with naltrexone treatment. Non-physically dependent opioid abusers were enrolled in a 12-week outpatient treatment research program in which they received weekly counseling and naltrexone (100 mg on Mon and Wed and 150 mg on Fri, with 36 total available doses during the study). Subjects were randomized to three treatment groups: 1) Contingent (N = 19) - vouchers earned for ingesting naltrexone; 2) NonContingent (N = 19) - vouchers given at rates and values matched to the Contingent Group but independent of naltrexone ingestion; and 3) No Vouchers (N = 20) - no vouchers were available. The vouchers were exchangeable for goods and services. Mean treatment durations were (mean ± S.E.M.): Contingent Group - 7.4± 1.2 weeks; NonContingent Group - 5.3 ± 1.0 weeks; No Voucher Group - 2.3 ± 0.7 weeks. The No Voucher Group had significantly shorter treatment retention than the NonContingent Group, but retention was not different between the Contingent and NonContingent Groups. In contrast, the Contingent Group ingested significantly more naltrexone doses than both the NonContingent and No Voucher Groups: 21.3 ± 3.5 doses vs. 11.3 ± 3 and 4.8 ± 1.7 doses, respectively. The Contingent Group also ingested significantly more consecutive naltrexone doses than both the NonContingent and No Voucher Groups: 19.6 vs. 8.4 vs. 3.0 doses, respectively. Opiate and cocaine use tended to be lower in the Contingent Group compared to the NonContingent Group. These preliminary analyses suggest that the availability of the vouchers maintained subjects in treatment; however, the vouchers given contingent on naltrexone ingestion selectively increased adherence to the naltrexone administration regimen.

EVALUATION OF COUPLES IN METHADONE MAINTENANCE TREATMENT RESEARCH

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Abstinence from illicit substances may be more difficult to achieve when couples seek treatment simultaneously. Entry into treatment as a couple could be mutually beneficial or detrimental, depending on the individual goals and degree of success of each patient. During a recent behavioral treatment research study in which the effects of contingency management in poly-drug using methadone maintenance participants was evaluated, sixty-four individuals (32 couples) out of approximately 350 participants acknowledged having a spouse/significant other enrolled in treatment at the same clinic. To determine the effect of simultaneous treatment in substance abusing couples, the outcomes of 100 participants who completed treatment were compared. Fifty participants which were part of a couple in treatment were matched with 50 participants who did not have a partner in treatment. Groups were matched on four criteria; drug of choice, random contingency management assignment, gender and ethnicity. Treatment compliance and outcomes in the two groups were compared on the following variables; treatment retention, drug use while in treatment, reason for discharge and type of followup treatment chosen at study completion. It was expected that couples participating in the study would remain in treatment, would use illicit substances more often, and would be less successful in transferring to non-research methadone maintenance programs or medically supervised withdrawal from methadone without returning to illicit drug use. The analysis did not find significant differences between the groups but did suggest a trend of worse outcome for couples (discharges due to incarceration and misconduct). Future studies will evaluate whether couples counseling of methadone maintenance participants will improve outcome.

A TOKEN ECONOMY INTERVENTION FOR METHADONE MAINTENANCE PATIENTS

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We examined the effectiveness of a token economy intervention for reducing illicit drug use among methadone maintenance patients. On admission, consenting patients were randomly assigned to the TOKEN (n = 31) reinforcement protocol or to standard treatment (STD, n = 31) at the Philadelphia VA Medical Center. For the 9-month duration of the intervention, TOKEN subjects could earn up to 40 tokens per week for the completion of tasks devised with counselors to approximate (or shape) treatment plan goals. They could earn another 40 tokens per week by submitting drug-free urine specimens. Tokens could be exchanged for treatment privileges (such as take-home medication doses) or reimbursement, at a rate of $.50/token, for expenses pre-approved by counselors and documented with bills or receipts. Urine specimens were collected twice a week; results were aggregated over 4-week intervals and served as the primary outcome measure. Complete data were available for the first 24 weeks of treatment. A repeated measures ANOVA on the number of drug-free urines submitted during each of 6 4-week intervals indicated no overall between-group differences, no change in results over time, and no differences in rates of change over time. Secondary analyses of ASI variables collected at intake, 12 and 24 weeks indicated no greater improvement for TOKEN subjects on composite scores in any problem area, although all subjects showed improvement in Drug and Legal problems. The results question the generalizability of a previous study in which subjects reinforced for treatment plan related tasks showed greater improvement than subjects receiving no incentives or subjects reinforced for drug-free urines. Ongoing analysis of data from the present study will focus on determining the factors contributing to the divergence from previous results.

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PROMOTING OPIATE AND COCAINE ABSTINENCE WITH CONTINGENT METHADONE TAKE-HOME INCENTIVES

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Methadone maintenance patients with high (>80%) rates of drug positive urines. are unlikely to become abstinent when 2 weeks of drug-free urines are required to earn methadone take-home incentives. This study investigates conditions under which abstinence from opiates and cocaine may be obtained in this group. Patients were screened while maintained on 60 mg methadone; those submitting >80% opiate and/or cocaine positive urines were selected and methadone dose was raised to 80-100 mg for those with evidence of continuing opiate use. Only patients who continued opiate and/or cocaine use with high dose methadone (N=30) were then randomly assigned to one of three interventions that varied conditions for initiating and reinstating take-home reinforcement during three times per week urine testing: 1) no take-homes available, 2) one drug-free urine required (daily), or 3) three consecutive drug-free urines required (weekly). Ten patients were assigned to each group. Percent of urines positive for opiates and/or cocaine during high dose methadone baseline was 92%, 90% and 95% for no take-homes, daily and weekly groups, respectively. During the four months of the intervention, these opiate and/or cocaine positive urine rates decreased by 4%, 19%, and 20%. Further, five individual patients in the contingent groups (5/20 = 20%), but only one in the non contingent group (1/10 = 10%), have shown four or more consecutive weeks of abstinence from opiates and cocaine. These findings demonstrate that methadone dose raise followed by take-home incentives can reduce opiate and cocaine use for severe polydrug abusing patients previously believed to be resistant to take-home interventions.

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USING BEHAVIORALLY CONTINGENT PHARMACOTHERAPY IN OPIOID ABUSERS ENHANCES TREATMENT OUTCOME

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Preliminary results are presented from an ongoing six-month clinical trial evaluating the efficacy of making continued methadone maintenance contingent on attending all weekly scheduled individual and group counseling sessions. A total of 73 opioid abusers have completed the first 90-days of randomized treatment in the Experimental (N=35) or Control (N=38) conditions. Random assignment to treatment condition followed a four week baseline evaluation and stratification on admission ASI drug use score, baseline cocaine use (weekly urine results), psychiatric profile (*i.e.,* lifetime psychiatric diagnosis), and demographic characteristics (*e.g.,* gender, minority status). Following baseline evaluation, identical criteria were used in both groups to determine intensity of the weekly counseling schedule. More intensive weekly counseling was scheduled for patients with evidence of recent drug or alcohol use *(i.e.,* positive urine results) and/or counseling noncompliance (*i.e.,* missed counseling sessions). The highest amount of weekly counseling was eight hours (*i.e.,* Level 3). The Experimental group was informed that continuation of methadone therapy was contingent on attending scheduled weekly counseling sessions (routine and enhanced). The Control group was told that continued methadone therapy was independent of counseling attendance, though they were regularly encouraged by counselors to attend scheduled sessions. Primary outcome measures include rates of treatment attrition, counseling attendance, and drug use. There were no significant group differences on demographic measures, baseline drug use, or lifetime history of psychiatric comorbidity. As per study design, groups did not differ on mean methadone dose during the study (58mg). Significant outcome differences were found. Relative to Controls, patients in the Experimental condition had higher rates of counseling attendance (34% vs. 85%, $p<.001$), lower rates of weekly urine specimens positive for opioids (40% vs. 23%, $p< .03$) and cocaine (48% vs. 30%, $p<.06$), and a lower rate of attrition (19% vs. 10%, NS). These results support making continued maintenance on methadone contingent on attending routine and enhanced counseling sessions.

PATIENT RETENTION IN MOBILE AND FIXED-SITE METHADONE MAINTENANCE TREATMENT

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Hypothesis: Patients in mobile methadone treatment will be retained for longer periods than patients in fixed-site methadone treatment. Subjects: N=399 patients enrolled in Baltimore';; Mobile Health Services (MHS), an outpatient mobile methadone program were compared to N=1588 patients in six selected Baltimore fixed-site methadone programs. Procedures: The Individual Assessment Profile (IAP) provided data on MHS patient characteristics. Fixed-site program patient data were obtained from the Maryland Substance Abuse Management Information System (SAMIS). Using Cox regression analysis, retention was analyzed separately for N=664 fixed-site patients who resided in MHS targeted zip codes (MHSZIPS) and N=924 fixed-site patients who resided in other zip codes (OTHERZIPS). Results: MHS patients were retained for a median of 15.53 months in comparison to 3.90 for MHSZIPS and 6.27 for OTHERZIPS fixed-site patients, ($p<.001$). More arrests, more frequent cocaine use and lower family income, which predicted shorter retention, were generally more prevalent among patients from MHS served zip code. The results were consistent with findings by Brady *et al.,* (in press) suggesting that MHS provided greater access to services through reductions in travel time and transportation cost. Conclusion: Mobile methadone treatment may increase patient retention. Footnotes:

1. Mr: DeSmet is now with Columbia University, New York, NY.

References:

Brady, J.V. Besteman, K.J. and Greenfield, L. (in press) Evaluating the effectivenss of mobile drug abuse treatment. J.A. Inciardi, F. Tims, and B. Fletcher (ed). Westport ct: Green wood.

A PHARMACOLOGIC PROFILE OF SMOKED HEROIN AND COCAINE IN HUMANS

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The route of drug administration is known to be an important factor in determining the amount and speed of drug delivery to effector sites and hence, the abuse liability of drugs. Although an increase in the use of the smoked route as a mode of illicit drug self administration has been documented in recent years, only little information is available on the pharmacokinetic and pharmacodynamic profile of smoked heroin and cocaine. This research was designed to be an integrated pharmacological study of these drugs in humans. Volunteers resided on a closed clinical research unit for the study duration. Smoked drug was administered by a computer controlled smoking device which delivered a dose in a single puff with minimal pyrolysis and no loss as side stream smoke. Subjects were administered four smoked and four intravenous doses of heroin or cocaine in an ascending dose design with random placement of placebo. Physiological, subjective and performance measures were collected concurrently with biological samples. Data indicated that the pharmacological effects produced by smoked heroin (N=2) were similar to those produced by intravenous administration. Pharmacological effects after smoked cocaine (N=7) were linearly correlated with cocaine plasma concentrations. The smoked route proved to be an effective means of drug delivery for both heroin and cocaine. This mode of drug delivery could become popular with heroin users in a similar manner as seen with cocaine.

DAILY ACTIVITIES OF COCAINE USING METHADONE PATIENTS

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An exploratory study of 18 inner-city methadone patients, who continued to use cocaine despite recent participation in a cocaine treatment program, reported on their hourly activities over a period of nine consecutive days. All subjects were unemployed and 56% male; 89% reported using crack, 45% sniffed and 11% injected cocaine. The most frequent daily activities were: sleeping (Mean= 9.8 hours/day), watching TV (5.0 hours/day), substance and/or alcohol use (2.7 hours/day), socializing (2.1 hours/day), food preparation/eating (1.7 hours/day), and attendance at methadone program (1.0 hour/day). Crack was the most frequently used drug followed by powder cocaine. On the days that crack was used, the mean number of hours spent smoking crack was 3.70, and on days that powder cocaine (sniffing and/or injecting) was used, the mean number of hours was 3.17 hours. A weekend effect with weekly drug usage being highest on Saturday and lowest on Sunday, replicates our prior report on this effect. In general, episodes of powder cocaine and crack use took place over most of the day, but increased dramatically after 5 PM and stayed high until about midnight. The social context of crack and powder cocaine was shown to vary: crack smoking was reported to occur with equal frequency whether alone or with others; powder cocaine was more likely to be used when alone. These preliminary data suggest that, for these users, their days are restricted to either ubiquitous self-maintenance or passive activities (*e.g.,* sleeping, eating, watching TV).

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INTENSIVE OUTPATIENT TREATMENT FOR COCAINE-DEPENDENT METHADONE MAINTENANCE PATIENTS

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Cocaine dependence often undermines the efficacy of methadone maintenance treatment. In this report we present preliminary data in our ongoing evaluation of the provision of concurrent intensive outpatient treatment for cocaine- dependent methadone patients in our University-based programs. Thus far, 23 subjects who met DSM-IV criteria for cocaine dependence and were enrolled in our Methadone Treatment Program (MTP) have been treated in the Intensive Program. This program consists of a structured 20 hour per week psychosocial treatment of at least four weeks duration. The program is located a few blocks from the MTP and has separate staff. Patients receive group cognitive-behavioral therapy, drug education, occupational therapy, individual counseling and case management, as well as psychiatric and medical assessment. The mean age of the subjects was 36 years, 14 (61%) of the subjects were female, and 21 (91%) African-American. The subjects were on our MTP for a mean of 1.5 years, their mean dose was 70 mg, and 21 (91%) had a history of cocaine use prior to enrollment in the MTP. Their mean ASI composite scores were: drug .18; alcohol .03; employment .87; family .08; legal .02; medical .33; and psychiatric .11. Ten (43%) injected, six (26%) smoked and seven (31%) snorted cocaine. Subjects attended au average of 16.6 sessions. Nine of 23 (39%) subjects successfully completed the program, eight of whom were female. The females had a significantly higher chance of completing the program than males (Fisher's Exact Test p=<0.04). It is possible that this was due to small sample size, or the preponderance of female case managers in the intensive program. There was no difference in the rate of successful completion by route of ingestion (Chi-square), years of cocaine use (t test) or ASI drug use composite score (t test). Intensive outpatient treatment can be helpful for cocaine dependent methadone patients. Further study should examine ways to improve outcomes, such as refinement in matching patients to specific types of programming.

THE ACUTE EFFECTS OF INTRANASAL COCAINE DIFFER IN TOBACCO SMOKERS AND NON-SMOKERS

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Tobacco cigarette smoking is more common among cocaine-dependent individuals than in the general populaton. However, it is unclear whether there is a pharmacological basis for this pattern of polydrug abuse. The present study was conducted to determine if the acute effects of cocaine differ in tobacco smokers as compared to nonsmokers. Healthy, male and female occasional cocaine users provided informed consent and volunteered to participate in this study. Subjects were placed into one of the following groups: nonsmoker, < 1 pack/day and <1 packday. Each subject served as his/her own control and was tested under double-blind conditions on two separate experimental sessions in which they received either 0.9 mg/kg cocaine or placebo via the intranasal route; studies were separated by a least one week (males) or one month (females). Dependent variables included: heart rate, blood pressure, skin temperature, the Addiction Research Center Inventory (ARCI), visual analogue scales (VAS), subjective reports of drug detection and euphoria/dysphoria and plasma cocaine levels. Compared to nonsmokers, male smokers detected cocaine's effects faster, had a shorter duration of effect and had fewer euphoric events. In addition, cocaine-induced tachycardia was markedly attenuated in the heavy smokers. In contrast, female smokers had more euphoria than non smokers. These data demonstrate that many of cocaine's effects are attenuated in male tobacco smokers. It is possible that this profile of effects may alter a smoker's early experience with cocaine. ACKNOWLEDGEMENTS: Supported by NIDA Grants DA00115 and DA03994.

COCAINE USE CAN INCREASE CIGARETTE SMOKING

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While the vast majority of cocaine abusers are also cigarette smokers, the relationship between cocaine use and cigarette smoking is poorly understood. The current report provides data from several studies that were designed to assess whether acute cocaine use increases rates of cigarette smoking. The first study examined a biochemical marker of cigarette smoking (cotinine) among cocaine-dependent outpatients who self-reported smoking more cigarettes when using cocaine. Cotinine levels were significantly elevated when patients used cocaine compared to when they did not use cocaine (cocaine use was verified via urinalysis). The second study examined cocaine self-administrations effect on cigarette smoking as a function of the dose of cocaine ingested. The number of cigarettes smoked increased as the amount of cocaine ingested increased. The final study examined the effect of administering 100 mg of cocaine or 100 mg of active placebo (96 mg lactose + 4 mg cocaine) over a 20 minute period on subsequent cigarette smoking. The majority of the subjects smoked more cigarettes following cocaine administration than following placebo administration. Considered together these results provide compelling evidence that acute cocaine ingestion increases cigarette smoking.

DIFFERENTIAL EFFECTS OF WITHDRAWAL ON NEUROCOGNITIVE FUNCTIONING IN COCAINE AND COCAINE AND ALCOHOL ABUSERS

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The differential effects of withdrawal on neurocognitive functioning were examined in a group of 14 cocaine abusers and 13 abusers of both cocaine + alcohol. The two groups met DSM-III-R criteria for only cocaine dependence/abuse, or for both cocaine and past or current alcohol dependence/abuse, respectively. All participants were admitted to the NIDA-IRP inpatient research unit for 30 days. A battery of neurocognitive tests were administered within three days of admission (baseline) and on the 28th day after admission. Drug free status was confirmed by random urine testing during the 30 day stay. The two groups were similar on age, education, Shipley IQ, race, gender and handedness. At baseline, the mean neurocognitive test performance of the two groups was not significantly different in 15/16 tests. However, after 28 days of withdrawal, the cocaine + alcohol group showed greater improvement on 10/16 of the tests, relative to the cocaine group. A within group comparison showed that the cocaine + alcohol group showed significant improvement ($p < 0.05$) on 5/16 tests while the cocaine group improved on 2/16 tests. Thus, withdrawal of drug using individuals for one month caused different changes in the neurocognitive performance of users of cocaine in comparison to that of users of cocaine plus alcohol. These results suggest that the additional use of alcohol or of any other drugs needs to be fully assessed when evaluating possible neurocognitive sequelae from specific drugs of abuse. The additional use of alcohol with other drugs of abuse may compound or negate any effects of these drugs on neurocognitive performance. These results also stress the need for paying close attention to the selection of research subjects for studies pertaining to the neurocognitive effects of cocaine or any other drug of abuse.

SUBJECTIVE EFFECTS OF INTRANASAL COCAINE IN MALES WITH AND WITHOUT A FAMILY HISTORY OF ALCOHOLISM

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Despite the number of studies suggesting an association between a positive family history of alcoholism and a higher vulnerability to developing alcoholism, there is little information on the relationship between such family history and altered responsiveness to other drugs of abuse, especially simulants. Fourteen healthy, male occasional cocaine users with (FHP) and without (FHN) a family history of alcoholism provided informed consent and volunteered to participate in this study. Each subject served as his own control and was tested under double-blind conditions on two separate experimental sessions in which they, received either 0.9 mg/kg cocaine or placebo via the intranasal route; studies were separated by at least one week. Dependent variables included: heart rate, blood pressure, the Addiction Research Center Inventory (ARCI) and nine visual analogue scales (VAS). The results of the Z-factor repeated measures ANOVA (with family history of alcoholism and cocaine dose as the independent variables) indicate that FHP subjects scored slightly higher than FHN subjects on a number of VASs including how "Good", how "Happy", how "High", and how "Stimulated' they felt 10 minutes after cocaine. They also appeared to recover from cocaine's effects more rapidly than the FHN subjects. These preliminary data suggest that although the reinforcing effects of cocaine may differ slightly in individuals with a positive family history of alcoholism, these modest differences in cocaine effects are probably not sufficient to place FHP subjects at a higher risk for developing cocaine abuse.

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COCAINE EFFECTS ON BRAIN WAVE ACTIVITY IN SUBJECTS WITH AND WITHOUT A FAMILY HISTORY OF ALCOHOLISM

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In an attempt to identify family history positive (FHP) individuals at high risk for developing alcoholism, researchers have used the P3 component of the event-related potential (ERP) as a measure of cognitive processing following drug challenges. This study was conducted to determine if the P3 ERP can be used to detect cognitive processing differences in individuals with a family history of alcoholism after cocaine administration. Healthy male recreational cocaine users with (FHP, n=11) and without (FHN, n=11) a family history of alcoholism were studied following intranasal administration of placebo and 0.9 mg/kg cocaine. Subjects were presented with an auditory "oddball" ERP paradigm and measurements were obtained at baseline and at 10, 30 and 60 minutes after drug administration. The ERP data were co-registered with MRI data to more precisely identify the anatomical source of cocaine-induced alterations in brain wave activity. A two-way repeated measures ANOVA revealed that FH differences were most apparent in frontal electrode sites. FHN individuals had significantly increased P3 amplitudes compared to FHP at 10 minutes (lead F7) and at 30 minutes (leads Fz, F7 & F8) post drug administration. When FH was collapsed, a cocaine-induced decrease in P3 amplitude was found at 10 minutes compared to baseline (lead Pz), and shorter P3 latencies at 10 and 30 minutes compared to baseline (leads F7 & F8). These findings suggest that cocaine may exert different effects on cognitive processing in FHP and FHN individuals and suggest that the P3 ERP may be a useful electrophysiological marker to identify individuals more sensitive to drugs of abuse other than alcohol.

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THE DISCRIMINATIVE STIMULUS EFFECTS OF A COCAINE-ALCOHOL MIXTURE

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Despite the toxic effects of concurrent cocaine and alcohol use, the combination is widely co-used. One possibility for this co-use is that the combination produces a unique stimulus which is perceived as different from, or perhaps more euphoric than, either of its parent components. Because the concurrent presence of cocaine and alcohol leads to the formation of cocaethylene, a unique metabolite which reportedly shares a similar pharmacological profile as cocaine, cocaethylene has been suggested to underlie self-reports of greater euphoria (McCance-Katz *et al.,* Psychopharmacology, 111:39-46; 1993). To assess the nature and quality of the combination's subjective effects, the present experiment examined this interaction within a drug discrimination procedure. Specifically, 12 Long-Evans female rats were trained to discriminate the concurrent administration of cocaine (5.6 mg/kg) and alcohol (0.75 g/kg) from their vehicles under a FR20 schedule of water reinforcement. Generalization tests were performed to assess the level of mixture-appropriate responding to various doses of cocaine, alcohol and cocaethylene. Morphine was administered to assess the pharmacological specificity of the training stimulus. Cocaine and alcohol administered alone produced mixture-appropriate responding in a dose dependent manner. Cocaine substituted fully for the mixture training stimulus at 10 mg/kg. Although alcohol failed to produce criterion level (*i.e.,* $\geq$ 80%) mixture-appropriate responding, nearly half of the subjects tested met criterion at the training dose of alcohol or higher. Although cocaethylene failed to substitute fully for the training mixture, over half of the subjects tested at the dose which produced the greatest mixture-appropriate responding (*i.e.,* 18.0 mg/kg) fully generalized mixture control to cocaethylene. Morphine failed to substitute for the training mixture in any subject or dose tested with the exception of one subject. These results are consistent with other mixture discrimination studies in that the subjective effects produced by a combination appear not to be qualitatively different from those produced by its component elements.

THE INTERACTION OF COCAINE AND ALCOHOL: AN ASSESSMENT OF THE ROLE OF COCAETHYLENE

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Previous study from our lab found that ineffective doses of cocaine (or alcohol) enhanced the response-suppressing effects of alcohol (or cocaine). The mechanism underlying the increased effects of this combination has been speculated to be the formation of cocaethylene, resulting from the co-administration of cocaine and alcohol. Given that cocaethylene has been reported to possess similar pharmacokinetics as cocaine and to be behaviorally active, it is possible that the increased effect of cocaine and alcohol results from summating the response-suppressing effects of cocaine, alcohol and cocaethylene. The present experiment assessed this issue. Specifically, seven experimentally naive, water-deprived female rats were trained to respond on a FR20 schedule for a water reinforcer. The sessions consisted of four alternating cycles of 9-min lights-off during which time responding had no programmed consequences and 5-min lights-on during which time reinforcement was provided. Subjects were administered cumulative doses of cocaethylene, cocaine or alcohol at the outset of each lights-off period. Following this, they were administered an ineffective dose of cocaethylene prior to further dose-response assessments with cocaine or alcohol. Additionally, they were injected with ineffective doses of cocaine or alcohol prior to further dose-response assessments with cocaethylene. Cocaethylene, cocaine and alcohol alone produced dose-related decreases in responding. Further, the dose-response function for cocaethylene was shifted to the left by alcohol and cocaine. Similarly, the dose-response function for cocaine or alcohol was shifted to the left by cocaethylene. The analyses of isobolograms revealed that the interaction between cocaethylene and cocaine or cocaethylene and alcohol is simply additive in nature, suggesting that the increased effects of cocaine and alcohol may be due to the added effects of cocaine, alcohol and cocaethylene.

TREATMENT OUTCOME OF ALCOHOL-COCAINE DEPENDENT PATIENTS

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We conducted a retrospective comparison of cocaine dependent patients with and without concurrent alcohol dependence disorder on measures of substance use, addiction severity (ASI), and psychopathology (SCL-90, BDI), taken before, during, and after outpatient treatment for cocaine dependence. Recently hospitalized patients (n=32) all received the same 12-session outpatient relapse prevention treatment program, and were assessed at pretreatment ($t0$), weekly during treatment ($t1$- $t12$), posttreatment ($t13$), and 12- and 24-week follow up ($t14$, $t15$). DSM III-R diagnostic criteria were used to identify the "dual" (alcohol-cocaine) dependent (n=17) and "single" (cocaine-only) dependent (n=15) groups. At pretreatmcnt, cocaine only subjects reported significantly fewer past treatments and less days of alcohol use in the past 30 compared to the dual group. Drug screen results indicated a higher proportion of cocaine positive urines in the dual group during treatment ($t5$- $t8$), $p<.05$, with a similar trend at 12-week follow-up ($t14$), $p=.07$. Time related changes on the other outcome measures were tested using repeated Group (dual vs. single) by Time ($t13$, $t14$, $t15$) ANCOVAs, with $t0$ as a covariate. Significant Time effects were found on the ASI drug, family/social, and psychiatric scales, indicating overall reduction in problem severity following treatment. Significant Group effects were found for days of cocaine use (in past 30), ASI drug and employment scales, BDI and seven of the nine psychiatric symptom scales on the SCL-90. In all cases, scores across time points were higher in the dual group relative to the single group. In conclusion, both groups improved on important treatment outcome measures, however on most measures the cocaine-dependent only patients had better before and after treatment scores than the alcohol-cocaine dependent patients. These findings suggest that dually dependent patients do not respond as well as single dependent patients to a treatment that targets cocaine use only. ACKNOWLEDGEMENTS: Supported by NIDA grant DA-09262-02

INTERACTIONS BETWEEN THE DISCRIMINATIVE STIMULUS EFFECTS OF HEROIN AND COCAINE IN RATS

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Rats were trained to discriminate either heroin (0.56 mg/kg i.p.; N=6) or cocaine (5.6 mg/kg i.p.; N=6) from saline in a two-lever, food-reinforced, drug discrimination task. Heroin (0.032-1.8 mg/kg) dose-dependently increased heroin-appropriate responding in the heroin-trained rats, but elicited primarily saline-appropriate responding in the cocaine-trained rats. Cocaine (0.1-32 mg/kg) dose-dependently increased cocaine-appropriate responding in the cocaine-trained rats and generalized completely to heroin in two heroin-trained rats; however, cocaine elicited primarily saline-appropriate responding in the other four heroin-trained rats. The opioid antagonist naltrexone (0.01-10 mg/kg) blocked the discriminative effects of 0.56 mg/kg heroin but did not after the discriminative effects of 5.6 mg/kg cocaine. The dopamine-receptor antagonist flupenthixol (0.032-0.56 mg/kg) blocked the discriminative effects of both 0.56 mg/kg heroin and 5.6 mg/kg cocaine. When cocaine/heroin combinations were administered in the cocaine-trained rats, heroin (0.1-0.56 mg/kg) increased cocaine-appropriate responding elicited by low doses of cocaine in 3/6 cocaine-trained rats. In the heroin trained rats, cocaine (1-5.6 mg/kg) increased heroin-appropriate responding elicited by low doses of heroin in 115 rats, and cocaine alone generalized completely to heroin in this rat. However, in the other four rats, cocaine either did not alter the discriminative stimulus effects of heroin or decreased levels of heroin-appropriate responding elicited by high doses of heroin. These results suggest that the discriminative effects of heroin and cocaine in rats are pharmacologically distinct. When administered in combination, cocaine and heroin may enhance each other's discriminative effects in some subjects. Supported by a grant from the Ministry of Education and Science of Spain and by grants DA04059 and DA00101 from NIDA, NIH.

ANTAGONISM OF THE DISCRIMINATIVE STIMULUS EFFECTS OF ENADOLINE

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Receptor selective antagonists can be used to differentiate between opioid receptors which mediate particular effects of opioid agonists. In the present studies several opioids with antagonist actions were used to study the discrimiative stimulus (S^D) effects of kappa (κ agonists in squirrel monkeys trained to discriminate injections of enadoline (1.7-3.0μg/kg, i.m.) from injections of saline. To this end, the effects of the relatively non-selective opioid antagonist quadazocine (QUAD; 0.03-10mg/kg, i.m.), the κ--selective antagonist nor binaltorphamine (nBNI; 3.0-10mg/kg, i.m.) and the mixed action opioid nalbuphine (NALB; 0.3-30mg/kg, i.m) were determined. Results show that QUAD dose dependently shifted the enadoline S^D dose response (DR) curve to the right with an apparent pA2 of 6.92±0.42. NALB also dose-dependently antagonized the enadoline DR curve. The κ-selective antagonist nBNI produced antagonism of the S^D effects of enadoline and, additionally, the κ agonist U50488H. Peak effects for antagonism of the S^D effects of enadoline with each dose of nBNI were observed after 6 days, with average shifts in ED,, values of 0.7 (3.0mg/kg) and 1.2 (10mg/kg) log units. These results provide further evidence that the enadoline S^D is mediated via κ receptors and that the mixed action opioid NALB can serve as κ ı receptor antagonists. (Supported by USPHS DA03774, DA00499, MH07658 and RR00168).

PRELIMINARY ANALYSIS OF PLASMA CORTISOL IN COCAINE DEPENDENCE: TREATMENT WITH FLUOXETINE OR PLACEBO

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Preclinical data suggest that corticosteroids increase sensitivity to the reinforcing effects of cocaine. We retrospectively examined cortisol levels from 27 subjects before and after the first 8 weeks of a double-blind, placebo-controlled trial of fluoxetine treatment of cocaine abuse in methadone maintenance patients in order to determine whether the effects of fluoxetine on cocaine use are related to changes in cortisol levels. In addition, we attempted to obtain preliminary data on naturally occurring relationships between cocaine use and cortisol levels. In this study, plasma for cortisol levels was obtained between 7:45 A.M.-10:30 A.M.; individual subjects, however, had plasma obtained within 1 hour 15 minutes of their baseline collection time. Preliminary analyses indicate that in the placebo group, higher levels of cortisol at treatment week 8 are associated with less cocaine use at week 8. This relationship was not seen in the fluoxetine treated group. Also, a decrease in cocaine use between baseline and week 8 was associated with an increase in cortisol level in the placebo group but with a decrease in cortisol in the fluoxetine group. No clear relationship between cortisol at the end of week 8 and measures of cocaine use in the following week was found. These findings are more consistent with an effect of the frequency of cocaine use on cortisol level than a cortisol-induced change in subsequent cocaine use. In either case, the relationship between cocaine use and cortisol levels may be altered by fluoxetine treatment. These preliminary data are being further analyzed to control for concomitant drug use and potentially confounding factors. Implications for design of future cocaine treatment studies utilizing cortisol levels ate discussed.

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SCHIZOPHRENIA, COCAINE ABUSE AND NEGATIVE SYMPTOMS

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Between 15% to 60% of schizophrenic patients abuse psychoactive drugs (Richards, 1985; Mueser, 1990; and Dixon, 1991). At the PVAMC outpatient clinic the point prevelance is 24%. based on single urine drug screens (Stone, 1993) with cocaine as the frequently used substance. Research regarding the possible link between schizophrenia and substance abuse is needed in order to understand the mechanism(s) underlying the comorbidity of these diseases. our hypothesis is that there is a subgroup of schizophrenic patients whose cocaine dependence is correlated with the negative or deficit symtoms of their disease. Subjects for this 12- 18-week study were schizophrenic outpatients attending the depo neuroleptic clinic at the Philadelphia VAMC. at 2-3 week intervals, each subject provided a urine specimen for analysis in each visit and was rated by an investigator blind to their substance abuse diagnosis on the following instruments: Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), Brief Psychiatric Rating-Scale (BPRS), Modified Simpson/Angus EPS Scale, Hamilton Psychiatric Rating Scale for Depression (Ham-D), and urine for cocaine metabolite for a total of six visits in 2-3 week intervals. The results from 50 subjects have been collected and these data are currently being entered in preparation for statistical analysis.

THE HISTORY AND CURRENT ACTIVITIES OF THE DRUG EVALUATION COMMITTEE (DEC) OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (CPDD)

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ABSTRACT

From its inception in 1929 as a committee of the National Research Council of the National Academy of Sciences, to the present time, notwithstanding the various name changes which the organization has undergone, the CPDD has embraced the functions of the contemporary Drug Evaluation Committee (DEC). During the CPDD's initial 54 years, pharmacological, chemical, and clinical investigations of drugs of abuse were considered essential programs; indeed, the "CPDD" was formed for those purposes. The CPDD committee structure has been formalized over the last 20 years, and the DEC was established to continue the research and drug testing work which distinguishes the CPDD from other scientific organizations. Recently, CPDD reestablished itself as a membership organization and its members will ultimately decide the fate of the relationship between DEC and CPDD in the 21st century. This history of the DEC was written to reacquaint the members of the CPDD with the origins of this unusual committee, to inform them about its current activities, and to relate what services the committee offers to them. DEC members engage in methodological research and testing of drugs with analgesic, stimulant, depressant, and/or hallucinogenic actions, providing information relating to the physical dependence potential and abuse liability of these drugs to the pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, and the WHO. For the membership of CPDD, as well as to researchers throughout the world, DEC offers to determine the physical dependence potential and abuse liability of your interesting new or old analgesics, stimulants and/or depressants. This free public service by the DEC sets the CPDD apart from all other scientific membership organizations.

CPDD/DEC

"L état, c' est moi", said Louis XIV (Dulaure 1863). Louis XIV felt that he was indistinguishable from France. To the world, from 1929 to the mid- or late-1970's, the CPDD and DEC appeared to be similarly entwined. In the beginning there was the CPDD, and there were no subcommittees. The history of CPDD has been related in several publications (Acker 1995; Eddy 1973; May and Jacobson 1989). That history will not be repeated unless it relates to the DEC, and the term "CPDD/DEC" will be used to indicate the essentially synonymous character of CPDD and DEC during their earlier coexistence.

In the 1930's, those who became involved in drug testing and methodological research did so at the instigation of CPDD/DEC, and reported to CPDD/DEC. "Oversight" of this function was by the entire membership of CPDD/DEC, since analgesic drug testing (pharmacological and clinical) and chemical research were the main purposes, if not the only functions, of the CPDD/DEC. The members of the CPDD/DEC were those who were appointed (at the suggestion of the CPDD/DEC members) by the National Research Council (NRC) of the National Academy of Sciences (NAS). Many of those members served very long terms on the Board. CPDD members were not necessarily chosen for inclusion in the testing groups (although then, as now, many of those involved in the drug evaluation were also CPDD members at some point in their careers). As the CPDD evolved after the mid-1970's, the (sub)committee structure became essential for its expanded functions, and it was only then, more than 40 years after its formation, that DEC and CPDD could be distinguished. CPDD did not become a scientific membership organization until 1991. This article will describe the formation of the DEC and its transformation, while continuing its' testing and research functions for the past 67 years.

FORMATION OF THE DEC

The contemporary DEC is a direct descendent of the initial analgesic testing program of the Committee on Drug Addiction of the NRC, NAS (Acker 1995; Eddy 1973; May and Jacobson 1989). That testing (and research) program began in 1930 with the appointment of Dr. Nathan Eddy to direct CPDD/DEC pharmacology at the University of Michigan, a year after the CPDD itself was formed. Neither the original Committee of the NRC, NAS, nor its subsequent organizations, which bore slight modificatiors in name, were subdivided into subcommittees and this continued somewhat after the time CPDD became independent of the NAS in 1976 (with the possible exception of a "program committee" established in 1970). In the late 1970's, however, the forerunner of DEC became a committee of the Committee on Problems of Drug Dependence, and thus was a committee of a Committee. This unfortunate abundance of "committees" may have signaled a certain lack of imagination by the members of the CPDD, but the distinction between the CPDD and the committee was quite clear to the members, perhaps because so many of them had been CPDD members for a considerable time. More contemporary CPDD Board members tended to think of DEC as a subcommittee, but the committee (of a Committee) terminology was inextricably intermingled and confused until the CPDD became the College on Problems of Drug Dependence in 1991.

The history of the DEC is hardly distinguishable from the history of the CPDD in its early years. Nevertheless, the seed of DEC's ancestry can be traced to one of the original functions of the CPDD, the attempt to replace all addicting alkaloids by substitutes without addiction properties (White 1941). The search for a drug without physical dependence potential or abuse liability has taken on legendary aspects. The hunt began not long after the drug heroin, with the heralded magical properties, was discovered. Heroin was originally promoted as a non-addicting analgesic; it could relieve the clinical symptomatology due to withdrawal from the chronic use of morphine. We have come a long way since then. We have medication treatment agents which are very useful for the treatment of heroin abuse (e.g., methadone, LAAM, buprenorphine, naloxone, and naltrexone), and analgesics multi-thousands times more potent than morphine or heroin. We have agonists, mixed agonist-antagonists, and antagonists to all of the main types of opioid receptors, but the search for the "perfect" analgesic goes on. Medicinal chemists are the true believers; they know that they will find the "magic bullet".

The Committee on Drug Addiction (which can be considered the forerunner of CPDD and DEC) initiated a tripartite effort in 1930 which consisted of chemical work under the direction of Dr. Lyndon Small (who was sent to the University of Virginia), pharmacological testing (headed by Eddy, who was stationed at the University of Michigan), and clinical work (accomplished first at Fort Leavenworth, Kansas, and then at Lexington, Kentucky, in what became the forerunner of the contemporary Addiction Research Center, the intramural research arm of NIDA). In the early years of CPDD/DEC, chemistry, pharmacology, and human testing were blended (Acker 1995; Eddy 1973; May and Jacobson 1989). The DEC is now charged with the responsibility for only one of these three fields, pharmacology, now expanded to encompass research and testing of several types of dependence-producing drugs.

Small moved to NIH in 1939, followed soon thereafter by Eddy (NIDDK and NIH have their own history of name changes over the past several decades). The NIH to which Small and Eddy went eventually became NIDDK. Eddy retired from NIH in 1960, but acted as an NIH consultant until his death in 1973. Dr. Everette May continued the coordination work from 1967 until 1976, when he retired both as Coordinator of the Testing Program of CPDD/DEC and as Chief of the Medicinal Chemistry Section in the Laboratory of Chemistry, NIDDK, NIH. He now plays an important role in the DEC's analgesic testing program with Drs. Louis Harris and Mario Aceto in Richmond (Virginia Commonwealth University, Medical College of Virginia). May was a long-time member of the CPDD and, for several years, while acting as coordinator of CPDD DEC, was called a "consultant to the Executive Secretary for the screening programmes" (Minutes of the May 26, 1970 CPDD meeting). In 1975, May assumed the title "Coordinator of Testing Program". May was replaced as Coordinator in 1976, by the author of this article. All three managers of the drug evaluation function of the CPDD were rooted in what has become the Laboratory of Medicinal Chemistry, NIDDK, NIH.

During the 37 years in which Eddy coordinated this program (concurrently serving as Executive Secretary of the CPDD for 21 of those years) he did not have a particular title for the coordination role. Some time after Eddy retired, May (personal communication, 1995) asked Dr. Leo Hollister, then Chairman of the CPDD, for a suitable title and that assignment of a title ("Coordinator of Testing Program") formalized the separation of the activities of the CPDD and DEC. This division was one of the extensive changes in the CPDD in the early and mid-1970's

caused by Eddy's death in 1973 and by the severance of the CPDD from the NAS in 1976. The history of DEC as a committee clearly separated in form and function from CPDD, is a reasonably contemporary history.

THE TRANSFORMATION OF THE DEC

The name of this committee, as well as the name of the CPDD itself, has changed over the last 65 years. For over 50 years the forerunner of DEC, on the few occasions when it was distinguished from CPDD, was called (in the Minutes to CPDD Board meetings), the "Drug Dependence Research Program", "Drug Dependence Research Program (Screening)", "Drug Evaluation Program", the "drug testing program", "drug screening program", and the "Biologic Testing Program of the CPDD". During those 50 years it focused mostly on analgesics. Until 1983 the forerunner of DEC was always referred to as a function, a "program" of the CPDD, not as a committee or subcommittee of the CPDD. Thus, during the late 1970's the title "Biological Coordinator of the CPDD, Inc." was used. The members of this program of DEC were informally considered those who were involved in the drug evaluation effort at Lexington, KY (which became the Addiction Research Center of NIDA), the University of Michigan, and Virginia Commonwealth University (Medical College of Virginia).

During the June, 1983 CPDD meeting, Dr. Joseph Brady, the CPDD Chair, announced the formation of a "Drug Testing Committee" for which I was to serve as Chair (with Drs. J. Woods, L. Harris, R. Schuster, J. Brady, C. Gorodetzky, and C. O'Brien as members), within which a clinical subcommittee would be established with O'Brien as Chair. Later that year, I served as Chair of an "Animal Testing Subcommittee" within the Drug Testing Committee of the CPDD. The clinical subcommittee was reformulated as the Human Testing subcommittee, with O'Brien as Chair. In 1984, this subcommittee was referred to as either the Human Testing subcommittee or the Clinical Testing subcommittee of the Drug Testing Committee of the CPDD. Thus, in 1983 the CPDD had a Drug Testing Committee enfolding two subcommittees, and one of these, the Animal Testing Subcommittee, was soon to expand to encompass the testing of stimulants and depressants.

The DEC included stimulants and depressants in its testing program because of concerns about the misuse of amphetamines and other stimulants, and the discovery that benzodiazepines, extensively used as anxiolytics, were subject to human physical dependence and abuse liability problems. In 1980, Woods raised the issue of expansion of the testing program to include sedatives and stimulants (Minutes of the June, 1980 CPDD meeting). In 1981, Brady formed a committee to examine this proposed expansion and, a year later, Woods and Schuster asked the Board to consider expansion of the DEC program to include stimulant/depressant testing facilities at the ARC in Lexington, the University of Chicago and the Johns Hopkins University; a committee was appointed to study the expansion. The report of this committee was discussed at a later CPDD meeting in 1982, and a CPDD grant was given to Dr. Chris Johanson at the University of Chicago to develop dependence-liability testing methods for sedative-hypnotics; the other cooperating units did not need funding. At the June, 1985 CPDD meeting, public announcement of the new testing facilities was suggested by Woods. At that point, there appeared to be two subcommittees (analgesic and stimulant/depressant) of the Animal Testing Subcommittee of the Drug Testing Committee (in 1984, the Human Testing Subcommittee was being referred to as a Committee, and was seen to be separate from the Drug Testing Committee). The membership of the stimulant/depressant testing groups changed during the ensuing years and, at present, the stimulant/depressant testing centers are located at the University of Mississippi, Louisiana State University, and the University of Michigan.

During 1985-1986, the CPDD established "standing committees" and "working committees". I was appointed Chair of a standing committee, the Drug Testing Program. A working committee was also formed that year, the "Coordinating Committee (Animal Testing Committee)" with Dr. Keith Killam as Chair, and Drs. M. Adler, T. Burks, R. Deitrich, C. Kornetsky, W. Martin, A. Takemori, and myself, as its members. The formation of such an "overseer" subcommittee had been recommended by Woods to the CPDD at its December, 1984 interim meeting, presumably to act to coordinate the roles of the various testing subcommittees and promote scientific discussions of the results of the testing programs among the involved groups. Dr. Theodore Cicero replaced Killam as Chair of the Coordinating Committee in 1987 and combined the Coordinating Committee with the Drug Evaluation Program, including both the animal and human testing committees. On June 27, 1988, at the CPDD Board meeting, the contemporary name of the Drug Evaluation Committee (DEC) was first mentioned.

NIDA grants (to Michigan) and contracts (to Richmond) had for some time covered most of the costs of the drug evaluation effort for analgesics (although during many of the initial years of work in Michigan and Richmond, the CPDD itself provided the necessary funding). A proposal for a grant to cover the work of the various groups involved with the testing of the stimulants and depressants was sent to NIDA in 1988 from Washington

University by Cicero, and it named the individual research units at the other institutions as grantees (University of Michigan, Medical College of Virginia (MCV)/Virginia Commonwealth University (VCU), and the University of Chicago). The stimulant/depressant five-year grant was awarded and begun in October, 1989. An annual DEC meeting to discuss the results of the work of both the analgesic and stimulant/depressant testing groups was announced in 1988, and has continued since then. At the December, 1990 CPDD interim meeting, it was noted that the "Animal Testing Subcommittee" name was still being retained to avoid confusion on the part of submitters of drugs, but that the overall group was the Drug Evaluation Committee (DEC). Soon thereafter the "Animal Testing Subcommittee" name was discontinued.

By 1991, I was called Biological Coordinator for the DEC - not for the CPDD itself, but for a CPDD committee, and Cicero acted as the Chair of the DEC. Cicero continued as Chair until 1995, when the CPDD Board decided that all CPDD committees should be headed by a contemporary member of the Board. Dr. Robert Balster, current CPDD Chair, recently appointed Dr. James Smith, a CPDD Board member and, for the past few years, one of the representatives of the Board on the DEC, as the Chair of DEC for 1995 1996. Dr. Cicero has assumed the title of "Executive Secretary of the DEC". He coordinates the new grants recently obtained from NIDA for 1995-1999 which allow the testing and research of the stimulant/depressant groups, and I continue to coordinate the day-to-day activities of the analgesic and stimulant/depressant groups as Biological Coordinator of the DEC. At least three representatives of the CPDD Board and membership have been on the DEC for the past several years, as well as representatives from each of the testing laboratories.

The various name changes accorded the drug testing role and its coordination reflected the suggestions of the nearly continuous succession of committees formed to search for the CPDD's purposes and functions following the separation of the CPDD from the NAS in 1976. These purposes and functions necessarily evolved over the past 20 years, compelled by the major changes in the underlying sciences associated with the work of the CPDD, and are still in the process of being modified by the CPDD Board. In an almost continuous pursuit of the CPDD's raison d'être, from 1976 to the present time, the CPDD, and later its committees have been examined, analyzed, and scrutinized. Thus, a series of CPDD "oversight" committees have been appointed to evaluate the structure, function, and financing of the DEC over these past 20 years. The most recent of these was appointed at the 1995 CPDD Interim meeting in San Juan.

PURPOSES AND FUNCTIONS OF DEC IN A MEMBERSHIP ORGANIZATION

The main function of the DEC is to evaluate drugs for their physical dependence potential and abuse liability. That has really not changed over the years, although the methodology for doing so has evolved with the underlying sciences. At the University of Michigan in 1950, the methods for determining physical dependence potential of analgesics were studied by Dr. M. Seevers using single-dose-suppression studies and primary physical dependence in his primate screening program. The initial drugs evaluated were all potential analgesics, but a small program that enjoyed a brief existence (ca. 1968-1971), was started by Dr. G. Deneau at the University of Michigan, and continued at the Southern Research Institute in Birmingham, to evaluate the dependence potential of hypnotics and sedatives in a barbiturate-dependent dog model. Abuse liability became determinable with the establishment of methodologies of animal self-administration (the CPDD/DEC encouraged expansion to the testing of psychoactive drugs other than analgesics using monkey self-administration in 1971) and drug discrimination.

The CPDD with DEC have written reviews detailing procedures used for testing drugs for their physical dependence potential and abuse liability. The latest compilation of the state-of-the-art methodologies was developed and reviewed by members of the CPDD and the DEC in 1984 for a NIDA Monograph (The Committee on Problems of Drug Dependence, Inc., Brady and Lukas eds 1984). This established scientific criteria for testing drugs subject to abuse which have been accepted by regulatory agencies. The CPDD and the DEC have a long history of working together with NIDA to *"attain our mutual objective in broadening the knowledge base in this area"* (Durell 1984). The DEC continues to be the preeminent commiltee of CPDD engaged in this area of research. As Dr. Jack Durell (then Associate Director for Science, NIDA) noted in his Foreword (Durell 1984) to the Brady and Lukas NIDA Monograph, *"The ultimate objective is to develop and refine methods that will allow for the prediction of the human dependence or addiction potential of a compound."* and, *"the laboratory work necessary for the development of these testing procedures has also contributed to the identification and characterization of novel compounds and the elucidation of fundamental biobehavioral mechanisms of drug action."* Certainly, if, as Durell also noted, *"The CPDD can be expected to play a leadership role in providing a forum for the integration of the many scientific, social and legal issues involved in coping with the problems of*

human drug dependence", the DEC will be the committee of CPDD which would lead the effort of obtaining data on drugs of abuse in animals which can be used to study the human problem of drug abuse. The CPDD, using its DEC, is the only membership organization in this scientific area able to obtain scientifically validated data on drugs subject to abuse. Without DEC, the close relationship which has been formed over the past several decades between the CPDD, NIDA, FDA, DEA, and WHO, would surely be lessened. This has become one of the main purposes of the DEC in a membership organization, to further extend the depth of the established relationships between CPDD and governmental organizations by providing the tools which are needed for determining the abuse potential of drugs, and the data necessary for drug regulation.

THE CONTEMPORARY WORK OF THE DEC

It is important to note that the DEC is not a closed organization. The DEC is now simply an organizational structure which facilitates collaborative research on drugs of abuse by researchers in university groups with complementary techniques, structured to allow its members to openly discuss ongoing work. The DEC welcomes those who can complement and extend existing expertise. However, the evaluation. effort must be funded through grants and/or contracts, and assurance must be given that the DEC testing will receive the highest priority.

DEC members engage in methodological research and testing of drugs with analgesic, stimulant, depressant, and/or hallucinogenic actions, providing information relating to the physical dependence potential and abuse liability of these drugs to the pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, and the WHO. The DEC data have been used by NIDA, DEA, FDA, and WHO for the determination of the scheduling of drugs, have been used by researchers in their search for medications to treat drug abuse, and are often quoted in their publications. The work is done free of charge as a public service to the scientific community and governmental organizations.

DEC is one of the few organizations able to provide such information using predetermined, validated and published methodology in a completely independent and unbiased manner. The data which are obtained by DEC, under the auspices of the CPDD, are published within three years of receipt of the drug and examples of these publications can be seen in various NIDA Monographs (Aceto *et al.* 1995; Jacobson 1995; Winger *et al.* 1995; Woods *et al.* 1995), as well as in various journals (Aceto *et al. 1996;* Aceto *et al.* 1989; May *et al.* 1994).

The specific work offered by DEC is as follows:

Analgesics:

The following assays are carried out on analgesics at MCV/VCU under the direction of Drs. L. Harris and M. Aceto, with Drs. E. Bowman and E. May. Some, or all, of these studies may be carried out, depending on the supply of the sample and interest in the properties of the drug:

1) Antinociceptive and narcotic antagonist assessment - determined through the phenylquinone, tail-flick, hot-plate, and tail-flick antagonism vs. morphine assays in mice. Apparent pA_2 values are obtained on compounds of interest using the tail-flick assay.

2) Substitution and primary physical dependence using rat-infusion assays.

3) Single-dose-suppression and, if warranted, precipitated withdrawal and primary physical-dependence studies in the rhesus monkey.

4) Intravenous self-administration studies in the rhesus monkey.

5) Drug discrimination studies in the rat.

Other studies on analgesics are carried out at the University of Michigan under the direction of Dr. J. Woods, with Drs. F. Medzihradsky, C. Smith, and G. Winger. Some, or all, of these studies may be carried out, depending on the supply of the sample and interest in the properties of the drug:

1) Opioid receptor binding - The binding affinity of the tested compound is determined by assessing its binding selectivity in monkey brain cortex at the μ- (using [^{3}H]-DAMGO), δ- (using [^{3}H]-*p*-Cl-DPDPE), and κ-opioid receptor (using [^{3}H]-U69,593).

2) Mouse *vas deferens* - The effect of ligands on particular opioid receptors is studied in the electrically stimulated mouse *vas deferens* preparation. Concentrations of a drug ranging between 10^{-10} and 10^{-5} M are tested to determine an EC50 for the drug, and a maximum response for inhibition of the twitch is reported. ICI-174864, a δ receptor agonist, is used to determine whether a shift occurs in the dose-response curve. Naltrexone and norbinaltorphimine (a κ antagonist) are also used to see whether the ligand has interacted with individual receptor types. The compound is then examined as an opioid antagonist by determining its effect on the actions of sufentanil (a μ agonist), U50,488 (a κ agonist), and DSLET (a δ agonist).

3) Self-administration - Analgesic compounds are evaluated for their potential reinforcing effects in rhesus monkeys experienced with the intravenous opioid self administration procedure under fixed ratio schedules. Several doses of each test compound are evaluated for their capacity to maintain responding in each of three monkeys. Test drugs must be soluble in water to be evaluated for reinforcing effects.

4) Drug discrimination assays in normal rhesus monkeys discriminating between saline and a prototypic μ or κ opioid agonist, and in morphine-treated monkeys discriminating between saline and naltrexone.

5) Analgesic studies in rhesus monkeys using a warm water tail-withdrawal assay.

6) Respiratory function studies in unanesthetized rhesus monkeys breathing air or 5% CO_2 in air.

If a compound shows a lack of agonist effect in these assays but has significant affinity for the binding sites described above, it is likely to be an antagonist (competitive or noncompetitive). Its potency may be assessed readily in the morphine-treated monkeys discriminating naltrexone. Its selectivity as an antagonist for different opioid behavioral effects may be assessed (and compared to standards of reference) in the various assays described above.

Stimulants and Depressants:

The DEC presently offers evaluation of stimulant or depressant types of drugs using the following methodology.

1) Self-administration studies are carried out at the University of Michigan under the direction of Dr. G. Winger. Rhesus monkeys are trained to respond to a fixed ratio 10, time out 10, schedule of intravenous methohexital (0.1 mg/kg/inj) delivery. Test drugs are substituted for the barbiturate on a periodic basis. A range of doses of each test drug is studied in each of three monkeys. Drugs must be water-soluble to be evaluated in this procedure.

2) Drug discrimination studies are conducted at the University of Mississippi Medical Center under the direction of Dr. W. Woolverton. The discriminative stimulus properties of drugs are determined in rhesus monkeys trained to discriminate pentobarbital or d-amphetamine from saline. Benzodiazepines can be distinguished from other depressants by blocking with flumazenil. The amphetamines are blocked by raclopride.

Drug discrimination and physical dependence studies are also conducted at the Louisiana State University Medical Center in New Orleans under the direction of Dr. C. France. Test compounds are evaluated for their discriminative stimulus effects and for their effects on responding maintained by food and responding maintained by shock avoidance in rhesus monkeys; the monkeys are physically dependent on a benzodiazepine and discriminate between injections of vehicle and the benzodiazepine antagonist flumazenil. Compounds are studied for their ability to substitute for the flumazenil discriminative stimulus in benzodiazepine-treated monkeys (i.e., precipitate withdrawal) and also for their ability to attenuate flumazenil-lever responding in monkeys that are either acutely deprived of benzodiazepine or treated with an effective dose of flumazenil (i.e., reverse withdrawal).

3) If resources are available, the physical dependence potential of the drug will be determined at MCV/VCU, under the direction of Drs. G. Patrick and L. Harris. The procedures can include:

a) An assessment of activity in an inverted screen test, and spontaneous locomotor activity in mice;

b) Assessment of physical-dependence potential by substitution in pentobarbital-dependent rats using continuous, intraperitoneal infusion;

c) Primary-physical-dependence determination in rats, by infusion.

Data obtained under the auspices of the CPDD are held confidential until three years elapse from the time of receipt of the sample unless: (1) we are given explicit permission to publish such data sooner; or, (2) in the rare and unlikely event that a department, agency or instrumentality of the U.S. Government or the World Health Organization requests information on a specific compound in the interest of the public welfare (e.g., a scheduling decision). Should such a request be made, the submitter is notified. When any of these conditions pertain, the data obtained under the auspices of the CPDD and the molecular structure of the compound will be released. Information published does not include the source of the compound, the name of the submitter, or any biological data sent to DEC by the submitter.

CONTEMPORARY ORGANIZATION OF DEC

The DEC now has the formal structure mentioned above, a (rotating) Chair appointed by the CPDD Board, an Executive Secretary, a Biological Coordinator, and distinct sets of university-based investigators. Two sets of university-based researchers examine and do research on analgesics, and three or four university-based sets of researchers similarly work on the stimulant-depressant-hallucinogenic families of drugs. All of the members of DEC, with the exception of the fluctuating Chair and Board representatives, are involved with some facet of the DEC research or testing.

The Chair, as noted above, links the DEC and the CPDD, and reports to the CPDD Board. The Executive Secretary plans, organizes and is fiscally responsible for the annual DEC meetings, and for maintaining the link between the stimulant-depressant-hallucinogenic testing groups and their main funding organization, NIDA. The DEC Executive Secretary is also involved with the research of the stimulant-depressant-hallucinogenic testing groups.

The Biological Coordinator has the responsibility for obtaining drugs from pharmaceutical industry, academia, and governmental organizations, assigning them code numbers, assessing the obtained spectroscopic and thin layer chromatographic data to validate drug structure and purity, and distributing the drugs to either or both the analgesic and the stimulant-depressant-hallucinogenic testing groups. The samples are sent with only a code number, molecular weight, and solubility and toxicity data, if known. The thin layer chromatographic data are repeated before and after biological testing by May at MCV/VCU, to assure drug stability. Testing results from the DEC groups are sent to the Biological Coordinator who transmits them to the submitter of the drug, and occasionally aids the submitter with their interpretation. The data obtained from MCV/VCU are forwarded by the Biological Coordinator to the investigators at UM, and vice versa. Information on all of these drugs is maintained in a database by the Biological Coordinator, and, when requested, a report is given about DEC work to the Chair or Executive Secretary, or directly to the Board. Requests for release of the obtained information are sent to the submitter of a drug by the Biological Coordinator. The released data are compiled annually and the code numbers are translated into drawn molecular structures and sent to the testing group, with the chemical name of the drug, for their publication of the data in the NIDA Research Monograph of the CPDD Annual Scientific Meeting. A compilation of these data from a molecular structure-biological activity viewpoint is also published in that Monograph by the Biological Coordinator. Further, the Biological Coordinator, with the help of May, compiles the annually published data and sends them to the UM to update their public database on DEC-evaluated drugs. The Biological Coordinator is also occasionally involved with some of the scientific work of the testing groups.

THE FUTURE OF THE DEC

The CPDD is as concerned with science and politics now as the CPDD was when it began; it is just more costly and time-consuming now. Perhaps by force of personality and the relatively small scale of the governmental agencies which then existed, Eddy was able to coordinate CPDD/DEC to obtain data on drugs which he could use in his role of CPDD Executive Secretary to “suggest” appropriate scheduling of a drug to the proper governmental authorities. Analgesics were his passion, and he and his Committee members were quite apt at presenting their views and getting them accepted. It is much more difficult to get scientific viewpoints across to governmental agencies and politicians now. It requires a tremendous investment of time and resources, almost necessitating. the use of public relations groups. The CPDD must utilize some of its monetary resources and committees to assure that their membership organization’s viewpoint is recognized. These committees must appropriately change as

the organization's objectives change, and a changing cast of members are appointed to those committees who are suited to represent one or another of its objectives.

The DEC views itself as an organization which does its essential function as a public service for the CPDD, researchers, the public, and for governmental organizations. It is a rather unusual committee for a membership organization. Unlike other CPDD committees, it functions almost independently on tasks which are completed on a multi-year scale, and it (or its members) receives multi-year funding from resources outside the CPDD. DEC's objectives and members remain relatively constant. The *contemporary* CPDD has integrated DEC's functions into CPDD through Board appointment of a DEC Chair. This is unobjectionable and is, in fact, the way almost all contemporary organizations operate; but it is a significant deviation from the CPDD norm established during the initial half-century. In the beginning, there was no separation between CPDD/DEC; they were one and the same, and for 21 years one person, Eddy, spoke for both. The CPDD is now fully engaged in changing its structure and organization, and all of its committees are continuously reexamined for their suitability to the desired changes.

DEC is still needed, and will continue to be needed in the future. At this time there are few other organizations able to provide independent, unbiased, and publishable information on potentially abusable drugs as a public service to governmental organizations, pharmaceutical industry, and university researchers. The researchers providing the service do so with funding through NIDA, without which this testing program would be infeasible. CPDD provides an additional source of income Approximately 5% of the CPDD budget is used for DEC. The CPDD funds are given to each of the DEC university groups and are used for organizational purposes, to write reports for the Board, and to cover costs associated with specific CPDD purposes (i.e., reports to submitters, annual reports to the CPDD, reports to regulatory agencies, and the maintenance of the Michigan database).

NIDA has funded the various university researchers because of the excellence of their work. NIDA also has programmatic and political needs which are benefited by the existence of DEC. NIDA is one of three governmental agencies (with the FDA and DEA) charged with the determination of the scheduling of drugs subject to abuse. NIDA provides the scientific information necessary for scheduling decisions, and the DEC is one of the principal organizations used by NIDA to obtain the data. Further, DEC provides NIDA with scientific information about potential medications to treat drug abuse.

Insofar as the CPDD is concerned, DEC enables the parent organization to assume the role of providing information to U.S. governmental organizations, and to the WHO, pharmaceutical industry, and academia. For medicinal chemists, and for others who bear responsibility for gathering pharmacological data in the pharmaceutical industry, governmental organizations, or universities, the DEC offers to determine the physical dependence potential and abuse liability of interesting new or old analgesics, stimulants and/or depressants. These data gathered by the DEC provide publishable information. The Biological Coordinator can be reached by mail, fax (301-402-089), or e-mail (aej@helix.nih.gov) to answer any questions about the submission of compounds and about this free service. The DEC exists to provide this service to the members of the CPDD, as well as to interested scientists throughout the world. The scientific information provided by DEC in the course of its work enhances the prestige of the parent organization. The DEC is itself enhanced by the imprimatur of a long-standing organization devoted to the study of drugs subject to abuse.

This symbiotic relationship of DEC with CPDD, NIDA, DEA, FDA, and the WHO, is likely to continue in the near future. Probably, as long as the researchers involved with DEC maintain and extend the underlying sciences, and continue their excellent work, NIDA funding will continue. It is easy to predict that in the future new drugs will be found which will be abused, chemical relatives of older drugs will be synthesized and abused, and new medications will be examined for their utility in treating drug abuse. The necessity and usefulness of obtaining independent and unbiased information on all of these drugs will continue. The DEC has had a long and distinguished existence; its many members have rendered a public service for over 65 years. The members of the CPDD will make the final decision about the continuation of the relationship between CPDD and DEC in the 21st century.

REFERENCES

Aceto, M. D.; Bowman, E.; Butelman, E.; Harris, L.; Jacobson, A. E.; Mattson, M.; Medzihradsky, F.; Patrick, G.; Smith, C. B.; Winger, G. D.; Woods, J. H.; and Woolverton, W. Zipeprol: Assessment of abuse potential in animals. Drug and Alcohol Dependence in press, 1996.

Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence studies of new compounds in the rhesus monkey, rat and mouse (1994). In: Harris, L. S., ed. Problems of Drug Dependence 1994, vol. I, pp. 162-212, NIDA Research Monograph 152, Washington, DC, 1995.

Aceto, M. D.; Bowman, E. R.; May, E. L.; Harris, L. S.; Woods, J. H.; Smith, C. B.; Medzihradsky, F.; and Jacobson, A. E. Very long-acting narcotic antagonists: The 14 P-p-substituted cinnamoylaminomorphinones and their partial mu agonist codeinone relatives. Arzneimittelforschung 39:570-575, 1989.

Acker, C. J. Addiction and the laboratory. The work of the National Research Council's Committee on Drug Addiction, 1928-1939. Isis 86:167-193, 1995.

The Committee on Problems of Drug Dependence, Inc. In: Brady, J. V. and Lukas, S. E., eds Testing Drugs for Physical Dependence Potential and Abuse Liability, NIDA Research Monograph 52, Washington, DC, 1984.

Dulaure: History of Paris, p. 387, 1863. Dulaure asserts that Louis XIV interrupted a judge who used the expression, 'The king and the state,' by saying, 'I am the state.'", from Bartlett's Familiar Quotations (as found on the Internet: http://www.cc.columbia.edu/acis/bartleby/bartlett/).

Durell, J.: The Committee on Problems of Drug Dependence. Foreword. In: Brady, J. V. and Lukas, S. E., eds. Testing Drugs for Physical Dependence Potential and Abuse Liability, pp. V-VI, NIDA Research Monograph 52, Washington, DC, 1984.

Eddy, N. B.: The National Research Council Involvement In The Opiate Problem. 1928-1971, National Academy of Sciences, Washington, D.C., 1973.

Jacobson, A. E.: Biological evaluation of compounds for their physical dependence potential and abuse liability. XVIII. Drug Evaluation Committee of the College on Problems of Drug Dependence, Inc. (1994). In: Harris, L. S., ed. Problems of Drug Dependence 1994, vol. I, pp. 84-104, NIDA Research Monograph 152, Washington, DC, 1995.

May, E. L.; Aceto, M. D.; Bowman, E. R.; Bentley, C.; Martin, B. R.; Harris, L. S.; Medzihradsky, F.; Mattson, M. V.; and Jacobson, A. E. Antipodalα-N-alkyl (methyl-decyl)-N-normetazocines (2'-hydroxy-5,9α-methyl-6,7-benzomorphans): *in vitro* and *in vivo* properties. J Med Chem 37:3408-3418, 1994.

May, E. L. and Jacobson, A. E. The Committee on Problems of Drug Dependence: a legacy of the National Academy of Sciences. A historical account. Drug Alcohol Depend 23: 183-218, 1989.

White, W. C.: National Research Council Report of Committee on Drug Addiction 1929-1941 and Collected Reprints 1930-1941, National Academy of Sciences, Washington, DC, 1941.

Winger, G.; Woolverton, W. L.; Rowlett, J. K.; English, J. A.; Patrick, G. A.; Nader, M. A.; McDaniel, R. E.; Hawkins, W. T.; Massey, B. W.; Harris, L. S.; and Woods, J. H.: Progress report from the testing program for stimulant and depressant drugs (1994). In: Harris, L. S., ed. Problems of Drug Dependence 1994, vol. I, pp. 105-116, NIDA Research Monograph 152, Washington, DC, 1995.

Woods, J. H.; Medzihradsky, F.; Smith, C. B.; France, C. P.; and Winger, G. D.: Evaluation of new compounds for opioid activity. 1994. In: Harris, L. S., ed. Problems of Drug Dependence 1994, vol. I, pp. 117-161, NIDA Research Monograph 152, Washington, DC, 1995.

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BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XX. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (1996)

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PURPOSES OF THE DRUG EVALUATION COMMITTEE (DEC)

This Committee's purposes and activities were recently delineated (Jacobson 1997). In that review of the 67 year history of DEC, it was noted that DEC and CPDD, were indistinguishable during their initial 43 years of existence. DEC was considered one of the essential programs or functions of CPDD, but the committee structure of CPDD did not exist. The contemporary DEC is a direct descendent of the original analgesic testing program of the Committee on Drug Addiction of the National Research Council, National Academy of Sciences. It has only been within the past 20-25 years that the purposes and activities of DEC could be distinguished from those of CPDD.

DEC members are now involved with methodological research and the testing of drugs with analgesic, stimulant, depressant, and/or hallucinogenic actions, and they provide information relating to the physical dependence potential and abuse liability of these drugs to the pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, and the WHO. For the membership of CPDD, as well as to researchers throughout the world, DEC offers to determine the physical dependence potential and abuse liability of your interesting new or old analgesics, stimulants and/or depressants. The Biological Coordinator can be reached by mail, fax (301-402-089), or e-mail (aej@helix.nih.gov) to answer any questions about the submission of compounds and about this free service. This free public service by the DEC sets the CPDD apart from all other scientific membership organizations. The data which are 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.* 1996; English *et al.* 1996; Woods *et al.* 1996) as well as in various journals (Aceto *et al.* 1989; May *et al.* 1994).

MEMBERS OF THE DRUG EVALUATION COMMITTEE (DEC) AND THEIR RESPONSIBILITIES

The CPDD Board has assigned two of its members to DEC, Dr. J. Smith (Wake Forest University), the current Chair of DEC, and Dr. M. R. Johnson. Dr. T. Cicero (Washington University) is the Executive Secretary, and I serve as Biological Coordinator. Other members of DEC are directly involved with drug evaluation (Drs. L. Harris, M. Aceto, J. Woods, G. Winger, W. Woolverton, and C. France).

The Chair links the DEC and the CPDD, and reports to the CPDD Board. The Executive Secretary plans, organizes and is fiscally responsible for the annual DEC meetings, and for maintaining the link between the stimulant-depressant-hallucinogenic testing groups and their main funding organization, NIDA. The DEC Executive Secretary is also involved with the research of the stimulant-depressant-hallucinogenic testing groups.

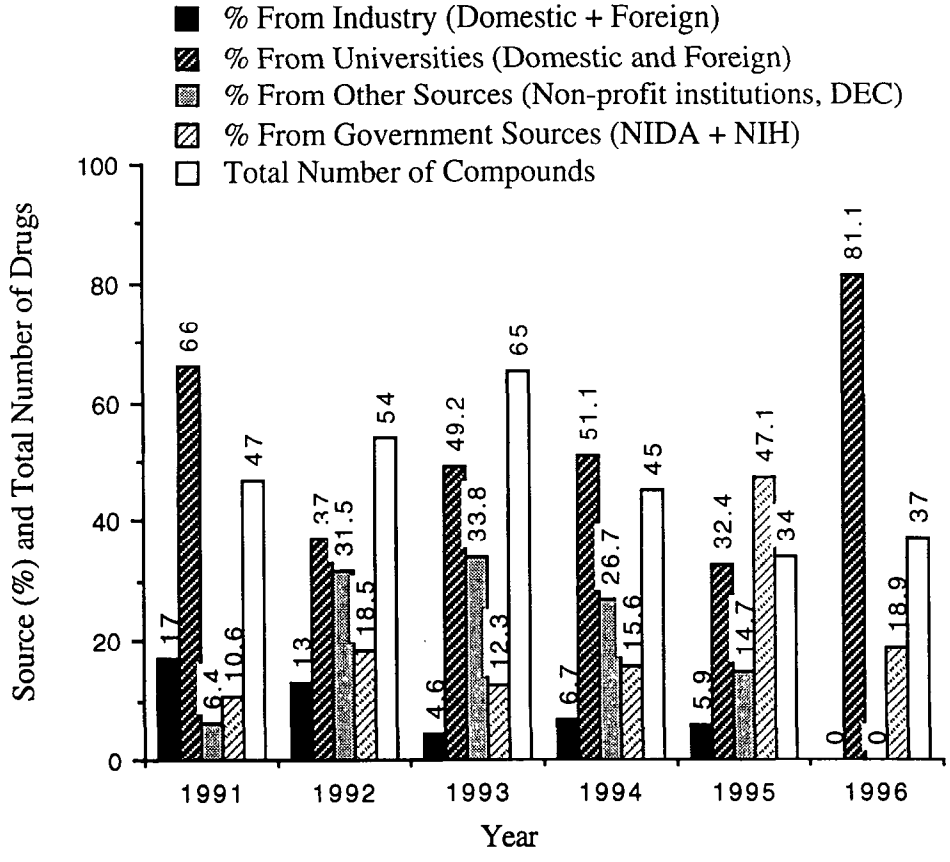
The Biological Coordinator has the responsibility for obtaining drugs from pharmaceutical industry, academia, and governmental organizations, assigning them code numbers, assessing the obtained spectroscopic and thin layer chromatographic data to validate drug structure and purity, and distributing the drugs to either or both the analgesic and the stimulant-depressant-hallucinogenic testing groups. The samples are sent with only a code number, molecular weight, solubility and, if known, toxicity data. The thin layer chromatographic data are repeated before and after biological testing by Dr. E. L. May at the Medical College of Virginia, Virginia Commonwealth University (MCV/VCU), to assure drug stability. Testing results from the DEC groups are sent to the Biological Coordinator who transmits them to the submitter of the drug, and occasionally aids the submitter with their interpretation. The data obtained from MCV/VCU are forwarded by the Biological Coordinator to the investigators at the University of Michigan (UM), and vice versa. Information on all of these drugs is maintained in a database by the Biological Coordinator, and, when requested, a report is given about

ADEC work to the Chair or Executive Secretary, or directly to the Board. Requests for release of the obtained information are sent to the submitter of a drug by the Biological Coordinator. The released data are compiled annually and the code numbers are translated into drawn molecular structures and sent to the testing group, with the chemical name of the drug, for their publication of the data in the NIDA Research Monograph of the CPDD Annual Scientific Meeting. A compilation of these data from a molecular structure-biological activity viewpoint is also published in that Monograph by the Biological Coordinator. Further, the Biological Coordinator, with the help of May, compiles the annually published data and sends them to the UM to update their public database on DEC-evaluated drugs. The Biological Coordinator is also occasionally involved with some of the scientific work of DEC (Jacobson 1997).

STATISTICS

The sources and number of compounds released for publication from 1991 - 1996 can be seen in Fig. 1. In 1996, two sources accounted for all of the examined drugs, universities and governmental. The university sources (81%) were both domestic (64.9%) and foreign (16.2%), and NIH researchers were the governmental source. One compound, obtained from NIDA, was released for publication after testing by the stimulant/depressant testing groups. The total number of compounds released for publication this year was about 10% greater than the number released last year, but less than in the previous years shown in Fig. 1. No drugs from industrial sources, nor from non-profit institutions or governmental sources other than NIH were released this year. The sources will become more disparate next year when several drugs are automatically released for publication.

FIG. 1. DEC ANALGESIC PROGRAM. PERCENT, TOTAL NUMBER, AND SOURCE OF EXAMINED DRUGS (1991-1996)



GROUPS INVOLVED IN DEC RESEARCH AND TESTING

The analgesic testing groups are based in MCV/VCU (Drs. L. Harris, M. Aceto, E. Bowman, and E. May) and at UM (Drs. J. Woods, F. Medzihradsky, C. Smith, and G. Winger). The stimulant/ depressant testing groups are at UM (Dr. G. Winger), the University of Mississippi (Drs. W. Woolverton and J. Rowlett), and Louisiana State University (Dr. C. France).

The DEC is not a closed organization; its organizational structure serves to facilitate collaborative research on drugs of abuse by researchers in university groups with complementary techniques, and it is structured to allow its members to openly discuss ongoing work. The DEC welcomes those who can complement and extend existing expertise. However, the evaluation effort must be funded from sources outside of CPDD, and assurance must be given that the DEC testing will receive the highest priority.

EXPERIMENTAL OBSERVATIONS

Table 1 lists the names and assigned NIH numbers of the compounds examined this year, and notes the specific table number where they appear. Tables 2 - 9 present the structures and a summary of the biological activities of compounds evaluated as analgesics, as obtained from Aceto *et al.* (1997), and Woods *et al.* (1997), and Table 9 summarizes the work of the stimulant/depressant groups on CPDD 0044. The compounds in Tables 2 - 8 are grouped according to their molecular structure (e.g., 4,5-epoxymorphanans, endoethanooripavines, 6,7-benzomorphans, etc.) in order to facilitate recognition of the relationship between their molecular structure and biological activity.

Five epoxymorphinans in Tables 2 and 3 (NIH 10826, 10827, 10825, 1083, and 10832) have been included in a manuscript on potential SPECT ligands (Kayakiri *et al.* in review). The C_6-iodo-substituted compounds were relatively μ-selective opioids, more potent in vitro and in vivo than their C_6-hydroxy relatives (10832 in Table 2 was estimated to be 300 times more potent than morphine in the SDS assay). Single-crystal x-ray analysis showed that the $C_6\alpha$-(10832 in Table 3) and C_6ß-iodine (10827 in Table 2) atoms were spatially closely located although the C-ring conformations of these compounds were quite different (twist-boat form vs. chair). The major epimeric conformational differences were not reflected in binding affinities to the μ-opioid receptor.

It is interesting to see the effect of a C_3-ether substituent in Table 3's 10844 and 10845. These drugs have identical substituents at C_{14} and are both N-cyclopropylmethyl-substituted epoxymorphinans. In the SDS assay, the C_3-cyclopropylmethoxy-substituted compound (10844) is a potent long-acting antagonist with minimal agonist properties. The C_3-propargylmethoxy-substituted compound (10845) does not suppress abstinence; it initially acts as a potent agonist, and this is followed by its action as an apparently irreversible antagonist. The effect of the C_3-cyclopropylmethoxy-substituent is different in the endoethanooripavine series, as can be seen with 10806 and 10807 in Table 4. Like 10844, neither of these drugs have much antinociceptive activity; however, both are weak, non-selective antagonists.

The epoxymorphinan 10849 in Table 3 exhibits a profile of action which could enable it to be a clinically useful analgesic. In rodent assays it was found to have reasonable antinociceptive potency; it was essentially morphine-like. Unlike morphine, however, it did not suppress abstinence in SDS studies in the rhesus monkey and it displayed weak narcotic antagonist properties in a precipitated withdrawal study. It is, thus, unlikely to induce opioid-like physical dependence in man.

The effect of a haloperidol-like side-chain (on nitrogen) in N-desmethylketobemidone (10834, Table 4) is remarkable. The potent opioid ketobemidone is transformed to a non-selective narcotic antagonist (as shown in the vas deferens assay), and was observed to have cataleptic activity in the SDS assay. The same N-side-chain in the piperidine 10873 (Table 4) does not modify the expected agonist activity, nor does it do so in the benzomorphan 10835 (Table 5). Thus, the N-side-chain cannot represent the portion of these opioid-like molecule which dictates agonist vs. antagonist behavior. However, it is also unlikely that the ketobemidone-like portion of the 10834 structure could induce antagonist behavior. Structural considerations would suggest that 10834 would be unlikely to have narcotic antagonist activity. The results in the vas deferens preparation, then, may not realistically reflect the in vivo activity of the molecule.

In the 4,5-epoxymorphinan or 6,7-benzomorphan series, compounds with an N-ally1 side-chain usually display narcotic antagonist activity. In order to explore the effect of that double-bond when situated further from the nitrogen atom, several longer-chain N-alkenyl norinetazocines were synthesized at MCV/VCU. The enantiomeric N-butenyl, N-pentenyl, and N-hexenyl compounds serve to illustrate that effect. In the (-)-series, N-butenylnormetazocine (10847, Table 5) was essentially morphine-like antinociceptively and promiscuous in receptor binding assays, with high affinity for κ- - and μ-opioid receptors. Its modest antagonist activity was seen in the TFA assay, and in SDS, where only partial suppression was observed. In contrast, the (-)-N-pentenyl analog (10852, Table 5) had only narcotic antagonist properties, and was somewhat weaker than 10847 in binding to κ- - and μ-opioid receptors. Unpredictably, the (-)-hexenyl analog (10855, Table 6) was not found to have narcotic-antagonist properties. It was morphine-like in antinociceptive assays and in the SDS assay. It is difficult to rationalize the activities of these normetazocines on structural grounds. That is, the (-)-N-allylnormetazocine (NIH 8773) (Aceto *et al.* 1990) is known to be a potent antagonist with minimal agonist activity. The (-)-N-butenylnormetazocine has now been found to be an agonist-antagonist, N-pentenyl a modest antagonist, and N-hexenyl a morphine-like agonist. The latter compound, with the largest side-chain, apparently cannot fit in an antagonist site in the various opioid receptors, or cannot convert an opioid receptor to an antagonist conformation.

Another (-)-normetazocine, 10864 (Table 7) with an N-hydroxyethyl side-chain, can interact with opioid receptors (especially κ,) but displays no agonist activity in antinociceptive assays or in the SDS. Perhaps it is insufficiently lipophilic to pass through blood-brain barriers. Further work will be done with the drug to determine whether it could be clinically useful as a peripheral analgesic. When the amino alcohol side-chain is converted to an amino ether (10863, Table 7), morphine-like in vivo and in vitro activity appear. The amino ether 10863 is a potent and selective κ–receptor opioid (e.g., μ/κ ratio = 16, and δ/κ ratio = 44).

γ-Hydroxybutyric acid (CPDD 0044, Table 9) was sent to the stimulant/depressant groups from NIDA, at the request of the DEA. The data from self-administration and drug discrimination assays allowed the prediction that the drug would have little, if any, abuse liability in man.

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.* 1997) and UM (Woods *et al.* 1997) reports.

1) MOUSE ED50/AD50: antinociceptive assays (sc injection); confidence limits are listed in the MCV report (Aceto *et al.* 1997).

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.* 1997)

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 1986) which were obtained under "-NaCl" (without NaCl) conditions.

BIND = subtype selective binding affinity using monkey brain cortex membranes (data from UM) (Woods *et al.* 1997). 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 deferens 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.* 1997).

3) IN VIVO: in the rhesus monkey.

SDS = single-dose-suppression (Parenthesized numbers = dose range studied, in mg/kg) (from MCV (Aceto *et al.* 1997), or UM prior to 1988).
NS = no suppression
CS = complete suppression
PS = partial suppression

Other Studies (if noted in the footnotes to the tables)

A) In Rat: RI = rat continuous infusion (data from MCV) (Aceto *et al.* 1997)

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. 1997)*
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.* 1997)
M-like = morphine-like effect.

3) PPD = primary physical dependence (data from MCV) (Aceto *et al.* 1997)

4) SA or SI = self-administration or self-injection (data from UM) (Woods *et al. 1997)*
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.* 1997)
NB = no effect
CS = complete substitution

6) MA = monkey analgesia (data from UM) (Woods *et al.* 1997)

7) RF = respiratory function (data from UM) (Woods *et al.* 1997)

Previous Reports

Previous work on a compound is noted using the year listed in the monograph title (*e.g.,* work cited as "1996" indicates that the work was included in "Problems of Drug Dependence 1996", which was published in 1997). 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.

REFERENCES

Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence studies of new compounds in the rhesus monkey, rat, and mouse. In: L. S. Harris, ed. Problems of Drug Dependence 1989, pp. 578-631, NIDA Research Monograph 95, Washington, D.C., 1990.

Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence studies of new compounds in the rhesus monkey, rat and mouse (1995). In: L. S. Harris, ed. Problems of Drug Dependence 1995, pp. 408-451, NIDA Research Monograph 162, Washington, D.C., 1996.

Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence studies of new compounds in the rhesus monkey, rat and mouse (1996). In: L. S. Harris, ed. Problems of Drug Dependence 1996, in press, NIDA Research Monograph, Washington, D.C., 1997.

Aceto, M. D.; Bowman, E. R.; May, E. L.; Harris, L. S.; Woods, J. H.; Smith, C. B.; Medzihradsky, F.; and Jacobson, A. E. Very long-acting narcotic antagonists: The 14 β-*p*-substituted cinnamoylaminomorphinones and their partial mu agonist codeinone relatives. Arzneimittelforschung 39:570-575, 1989.

English, J. A.; Rowlett, J. K.; Woolverton, W. L.; Patrick, G. A.; Hawkins, W. T.; Winger, G.; and Woods, J. H.: Progress report from the testing program for stimulant and depressant drugs (1995). In: L. S. Harris, ed. Problems of Drug Dependence 1995, pp. 452-468, NIDA Research Monograph 162, Washington, D.C., 1996.

Jacobson, A. E.: Biological evaluation of compounds for their physical dependence potential and abuse liability. IX. Drug testing program of the Committee on Problems of Drug Dependence, Inc. (1985). In: L. S. Harris, ed. Problems of Drug Dependence. 1985, pp. 385-398, NIDA Research Monograph 67, Washington, D.C., 1986.

Jacobson, A. E.: The history and current activities of the Drug Evaluation Committee (DEC) of the College on Problems of Drug Dependence (CPDD). In: L. S. Harris, ed. Problems of Drug Dependence 1996, in press, NIDA Research Monograph, Washington, D.C, 1997.

Kayakiri, H.; Jacobson, A. E.; Rice, K. C.; Rothman, R. R.; Aceto, M. D.; Bowman, E. R.; Harris, L. S.; Flippen-Anderson, J. L.; Xu, H.; May, E. L.; George, C.; Partilla, J. S.; and Becketts, K. Synthesis, single crystal analysis, in vitro and in vivo properties of 6α- and 6β-iodo-3,14-dihydroxy-17-methyl-4,5α-epoxymorphinans. Med Chem Res, in press, 1996.

May, E. L.; Aceto, M. D.; Bowman, E. R.; Bentley, C.; Martin, B. R.; Harris, L. S.; Medzihradsky, F.; Mattson, M. V.; and Jacobson, A. E. Antipodal α-N-alkyl (methyl-decyl)-N-normetazocines (2'-hydroxy-5,9'α-methyl-6,7-benzomorphans): in vitro and in vivo properties. J Med Chem 37:3408-3418, 1994.

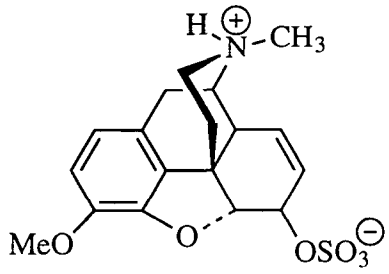
Woods, J. H.; Medzihradsky, F.; Smith, C. B.; Butelman, E. R.; and Winger, G. D.: Evaluation of new compounds for opioid activity (1995). In: L. S. Harris, ed. Problems of Drug Dependence 1995, pp. 377-407, NIDA Research Monograph 162, Washington, D.C., 1996.

Woods, J. H.; Medzihradsky, F.; Smith, C. B.; Butelman, E. R.; and Winger, G. D.: Evaluation of new compounds for opioid activity (1996). In: L. S. Harris, ed. Problems of Drug Dependence 1996, in press, NIDA Research Monograph, Washington, D.C., 1997.

TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

NIH#	NAME	TABLE #-Evaluator
10797	Codeine-6-O-sulfate zwitterion	2-MCV/UM
10798	Morphine-6-O-sulfate disodium salt	2-MCV/UM
10806	Buprenorphine-3-cyclopropylmethyl ether.HCl	4-MCV/UM
10807	Diprenorphine-3-cyclopropylmethyl ether.HCl	4-MCV/UM
10808	Naltrexone-3-cyclopropymethyl ether.HCl	2-MCV/UM
10815	(+)-4-[(αR)-α-(12S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC 80)	8-UM
10825	3-Acetoxy-6α-trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5 α-epoxymorphinan	3-MCV
10826	3-Acetoxy-14-hydroxy-6ß-iodo-17-methyl-4,5 α-epoxymorphinan	2-MCV/UM
10827	3,14-Dihydroxy-6ß-iodo-17-methyl-4,5 α-epoxymorphinan	2-MCV/UM
10831	3-Acetoxy-14-hydroxy-6 α-iodo-17-methyl-4,5 α-cpoxymorphinan	3-UM
10832	3,14ß-Dihydroxy-6 α-iodo-l7-methyl-4,5 α-epoxymorphinan	3-MCV/UM
10834	1-[3-(4-FIuorobenzoyl)propyl]-4-(3-hydroxyphenyl)-4-(1-oxopropyl)piperidine.HCl	4-MCV/UM
10835	(-)-5,9α-Dimethyl-2-[3-(4-fluorobenzoyl)propyl]-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10836	(+)-5,9α-Dimethyl-2-[3-(4-fluorobenzoyl)propyl]-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10842	Oxymorphindole.HCl	3-MCV
10844	14ß-(*p*-Chlorocinnamoylamino)-3-cyclopropylmethoxy-N-cycloproopylmethyl-7,8-dihydromorphinone	3-MCV
10845	14ß-(*p*-Chlorocinnamoylamino)-N-cyclopropylmethyl-3-propargylmmethoxy-7,8-dihydromorphinonc	3-MCV
10847	(-)-2-(3-Butenyl)-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan.HC1	5-MCV/UM
10848	(+)-2-(3-Butenyl)-5,9 α-dilnethyl-2'-hydroxy-6,7-benzomorphan HCl	5-MCV/UM
10849	N-Cyclopropylmethyl-7,8-dihydro-14ß-[3'(methoxycarbonyl)propenamido]normorphinone.oxalate	3-MCV
10852	(-)-5,9α-Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-benzomorphan.HCI	5-MCV/UM
10853	(+)-5,9α-Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-benzomorphan.HCI	5-MCV/UM
10854	1-(2-Pyrimidinyl)piperazine.2HCl	8-MCV/UM
10855	(-)-5,9α-Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-benzomorphan.HCl	6-MCV/UM
10856	(+)-5,9 α-Dimethy1-2-(5-hexenyl)-2'-hydroxy-6,7-benzonrporphan.HCl	6-MCV/UM
10857	(-)-2'-Acetoxy-5,9α-dimethyl-2-heptyl-6,7-benzomorphan.HCl	6-MCV/UM
10858	(-)-5,9 α-Dimethyl-2-heptyl-2'-methoxy-6,7-benzomorphan.HCI	6-MCV
10860	(-)-5,9 α-Dimethyl-2-heptyl-2-propionoxy-6,7-benzomorphan.HCl	6-UM
10862	(+)-2-(2-Cyanoethyl)-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6-MCV/UM
10863	(-)-5,9α-Dimethyl-2-(2-ethoxyethyl)-2'-hydroxy-6,7-benzomorphan.oxalate	7-MCV/UM
10864	(-)-5,9α-Dimethyl-2'-hydroxy-2-(2-hydroxycthyl)-6,7-benzomorphan.oxalate	7-MCV/UM
10865	(+)-5,9α-Dimethyl-2'-hydroxy-2-(2-hydroxyethyI)-6,7-benzornorphan.oxalate	7-MCV
10866	(+)-5,9 α-Dimethyl-2-(2-ethoxyethyl)-2'-hydroxy-6,7-benzomorphan.oxalate	7-MCV/UM
10868	Lofexidine[2-[1-(2,6-Dichlorophenoxy)ethyl]4,5-dihydro-1H-imidazole]	8-MCV
10869	(-)-2-Cyanomethyl-5,9α-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-MCV
10872	(+)-2-(5-Chloropenty1)-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan.HCI	7-MCV
10873	(+)-N-3-(*p*-Fluorobenzoyl)propyl-3ß-methyl-4-phenyl-4-propionyloxypiperidine.fumarate	4-MCV
CPDD 0044	γ-Hydroxybutyric Acid	9-UM/VMS

TABLE 2. 4,5-EPOXYMORPHINANS[a]



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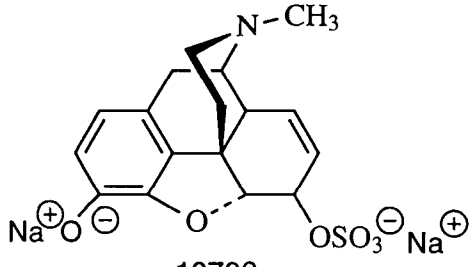

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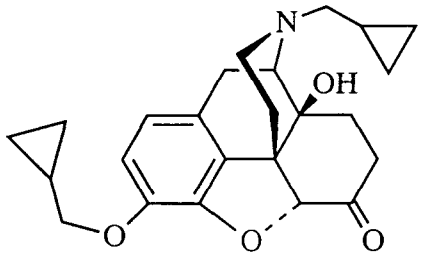

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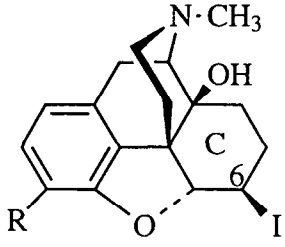


10826: R=OAc
10827: R=OH

	MOUSE ED50/AD60				IN VITRO		MONKEY
NIH #	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10797	I	I	I	I	3092	3470(96%)[A]	NE
10798	0.4	0.3	1.4	I	60	269(80%)[A]	CS (0.5xM)
10808	I	I	I	0.2	553	ANT[b]	NS[c]
10826	0.03[d]	0.02[d]	0.02[d]	I [d]	259[d,e]	287(90%)[A][d,f]	CS (20xM)[d]
10827	0.08	0.008	0.04	I	31[g]	63(100%)[A]	CS (60xM)

a) See text for explanation of column headings and abbreviations.

b) Weak, non-selective, antagonist.

c) Weak μ-antagonist.

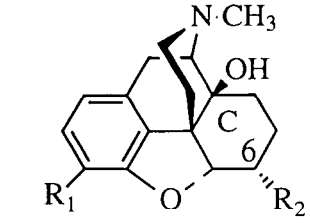
d) Previously reported - 1995.

e) BIND: μ=5.5, δ=319, κ=103 nM.

f) Partial μ-agonist, some κ-activity.

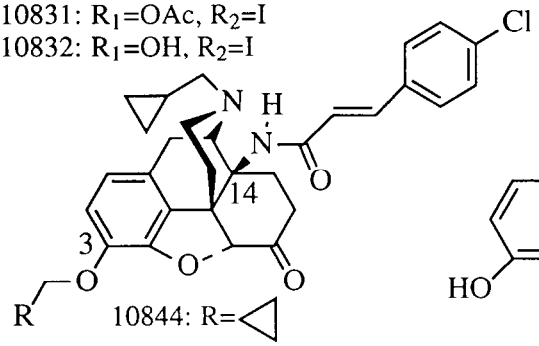
g) BIND: μ=0.9, δ=51, κ=13 nM.

TABLE 3 (CONTINUED). 4,5-EPOXYMORPHINANS[a]

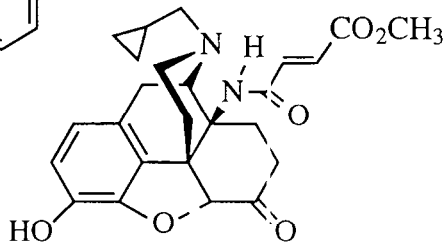


10825: R_1=OAc, R_2=OSO_2CF_3
10831: R_1=OAc, R_2=I
10832: R_1=OH, R_2=I

10842



10844: R=cyclopropyl
10845: R= C≡C

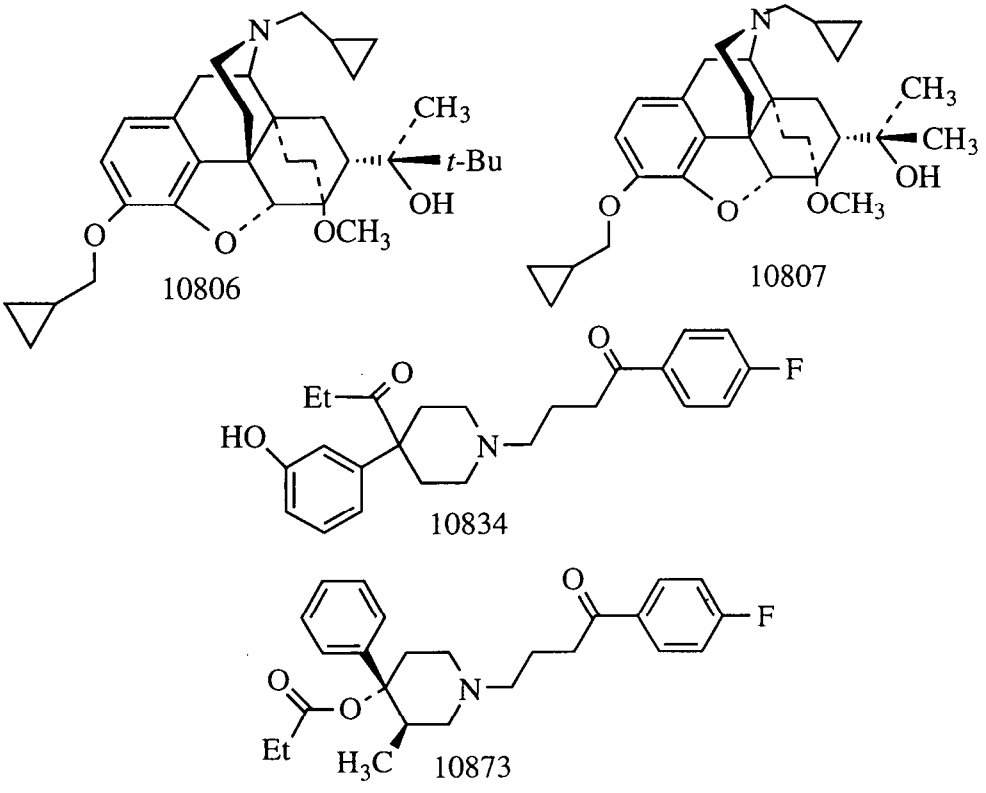


10849

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10825	0.22	0.04	0.14	I	1590[b]	276(91%)[A][b]	CS (20xM)
10831	0. 06[b]	0.009[b]	0.02[b]	I [b]	242[b,c]	6500(100%)[A][b,d]	CS (75xM)[b]
10832	0.02[b]	0.1[b]	0.02[b]	I [b]	40[b,e]	82(100%)[A][b]	CS (300xM)[b]
10842		I	I	I	BIND[b,f]	155(78%)[A][b,c,g]	NS[h]
10844	I						NS[i]
10845	0.26	0.26	1.2	I			CS (60xM)[j]
10849	1.8	1.5	1.2	I			NS, PW[k]

a) See text for explanation of column headings and abbreviations.
b) Previously reported - 1995.
c) BIND: μ=2.4,δ=238, κ=71 nM.
d) Weak μ- and δ-agonist.
e) BIND: μ=1.3,δ=79, κ=14 nM.
f) Previously reported - 1995; BIND: μ=157,δ= 2.29,κ=297 nM.
g) Previously reported - 1995; selective δ-antagonist.
h) Some reduction in withdrawal signs at 5 mg/kg.
i) Potent, long-acting antagonist.
j) Initial μ-agonist, followed by irreversible antagonist activity.
k) In PW: 0.1xN; less intense withdrawal than N; duration > N.

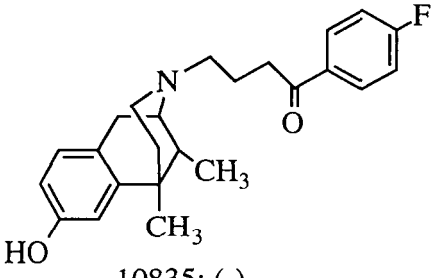
TABLE 4. ENDOETHANOORIPAVINES AND HALOPERIDOL-LIKE COMPOUNDS[a]



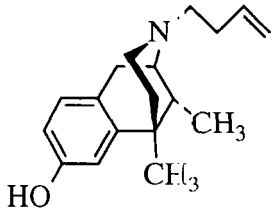
	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	H P	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10806	I	8.3	I	I	1060	ANT[b]	PS[c]
10807	I	I	I	I	990	ANT[d]	NS[e]
10834	I	0.48	I	I	BIND[f]	9.8(31%)[NA][g]	NS[h]
10873[i]	0.5	0.09	0.5	I			PS[j]

a) See text for explanation of column headings and abbreviations.
b) Weak, non-selective, antagonist; insurmountable at κ.
c) Weak, non-dose related suppression of withdrawal. Weak μ-activity.
d) Very weak, non-selective, antagonist.
e) Weak μ-antagonist with pronounced overt behavioral effects.
f) BIND: μ=l9,6δ= 180, κ=449 nM.
g) Weak, non-selective, antagonist.
h) Attenuated withdrawal due to severe cataleptic activity.
i) Racemate (NIH 10671) previously reported - 1991.
j) Higher doses might cause complete suppression.

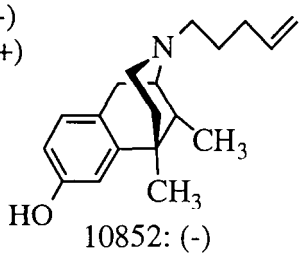
TABLE 5. 6,7-BENZOMORPHANS[a]



10835: (-)
10836: (+)



10847: (-)
10848: (+)

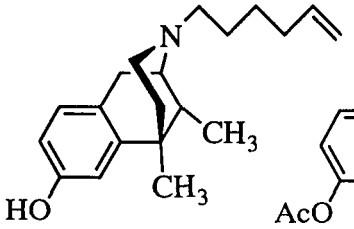


10852: (-)
10853: (+)

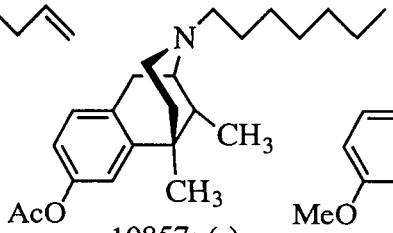
	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	HP	TF	TFA	PPQ	RBH	VD (nM)	SDS
10835	I	2.8	10.1	I	BIND[b]	1.2(100%)[NA]	PS[c]
10836	I	0.08	4.7	I	BIND[d]	66(100%)[NA][e]	NS[f]
10847	0.8	0.3	0.5	3.8	BIND[g]	103(84%)[A][h]	PS[i]
10848	I	1 7	I	I	BIND[j]	48(30%)[NA]	N S
10852	I	I	I	6.1	BIND[k]	537(100%)[A][l]	N S
10853	I	I	I	I	BIND[m]	308(16%)[NA]	N S

a) See text for explanation of column headings and abbreviations.
b) BIND: μ=l61, δ= 360, κ=153 nM.
c) Behavioral signs in mice and monkeys suggest neuroleptic properties.
d) BIND: μ=106, δ = >6000, κ=848 nM.
e) Very weak, non-selective antagonist.
f) Reduction of withdrawal scores at 5 mg/kg; possible neuroleptic.
g) BIND: μ=3, δ= 34, κ=1.5 nM.
h) Both μ- and κ-agonist.
i) Dose-related reduction of withdrawal, and signs seen with antagonists.
j) BIND: μ=1130, δ= >6000, κ=757 nM.
k) BIND: μ=12, δ= 93, κ=8 nM.
l) Both μ- and δ-agonist.
m) BIND: μ=>6000, δ= 4177, κ=>6000 nM.

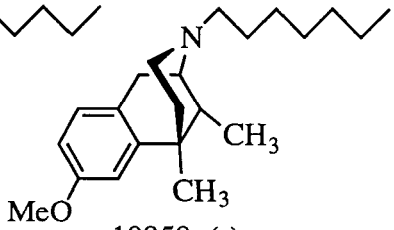
TABLE 6 (CONTINUED). 6,7-BENZOMORPHANS[a]



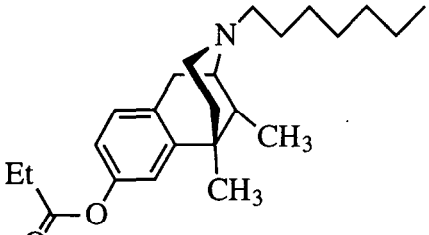
10855: (-)
10856: (+)



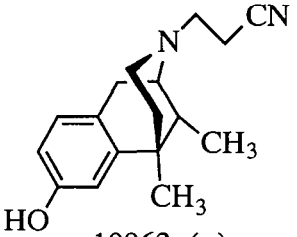
10857: (-)



10858: (-)



10860: (-)



10862: (+)

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10855	0.6	0.3	0.8	I	BIND[b]	175(100%)[A][c]	CS (1xM)
10856	I	I	I	I	BIND[d]	83(40%)[NA]	NS
10857	3	1.3	5.6	I	BIND[e]	246(93%)[NA]	NS[f]
10858	I	9.4	I	I			NS[g]
10860					BIND[h]	194(86%)[NA]	
10862	I	I	I	I	BIND[j]	3960(41%)[NA]	NS[k]

a) See text for explanation of column headings and abbreviations.

b) BIND: μ=18,δ= 98,κ=7 nM. Possible δ- -antagonist.

c) Both μ- and κ-agonist.

a) BIND: μ=816,δ= >6000,κ=492 nM.

e) BIND: μ=49,δ=,93,κ=60 nM.

f) Convulsions 10 min after cumulative dose of 15 mg/kg.

g) Ataxia, convulsions; no μ-like activity.

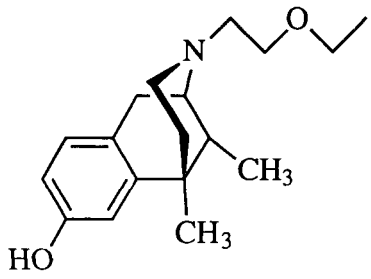
h) BIND: μ=28,δ= 47,κ=48 nM.

i) Decreased magnitude, but did not suppress twitch at any concentration; unusual agonist.

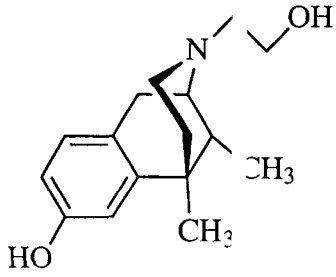
j) BIND: μ=>6000,δ= >6000,κ=223 nM.

k) Attenuated withdrawal; may have some antinociceptive activity.

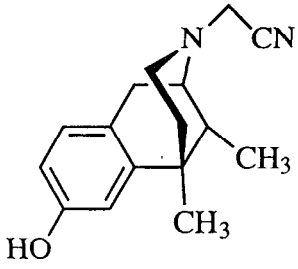
TABLE 7 (CONTINUED). 6,7-BENZOMORPHANS[a]



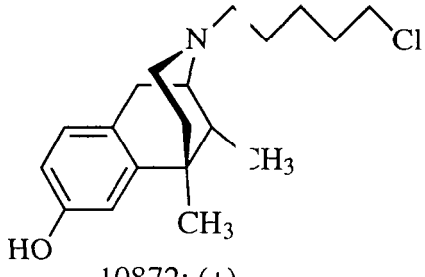
10863: (-)
10866: (+)



10864: (-)
10865: (+)



10869: (-)



10872: (+)

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	H P	PPQ	T F	TFA	RBH (nM)	VD (nM)	SDS
10863	0.85	0.85	1.08	I	BIND[b]	210(91%)[A]	CS (1xM)
10864	I	I	I	I	BIND[c]	1290(68%)[SA][d]	NS
10865	I	I	I	I			PS[e]
10866	I	I	I	I	BIND[f]	102(26%)[NA][g]	NS
10869	8.5	1.5	11.6	I			CS (0.5xM)
10872	I	4.6	I	I			

a) See text for explanation of column headings and abbreviations.

b) BIND: μ=42, δ= 115, κ=2.6 nM.

c) BIND: μ=41, δ= 316, κ=16 nM.

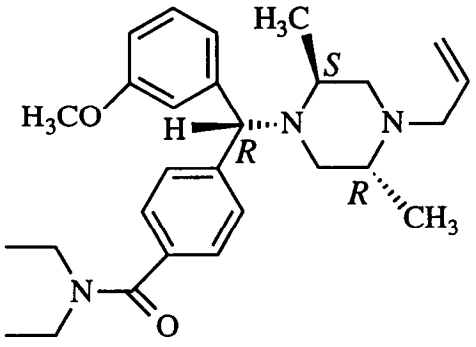
d) Weak δ-agonist.

e) Inverse dose-response; possible antinociceptive activity.

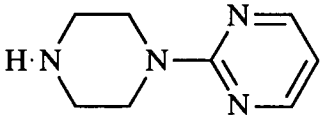
f) BIND: μ=956, δ= >6000, κ=629 nM.

g) Weak antagonist at μ and κ.

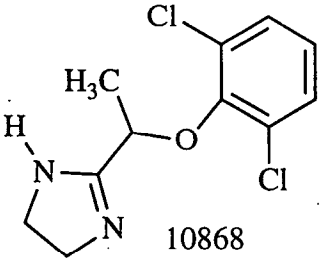
TABLE 8. MISCELLANEOUS[a]



10815 (SNC80)



10854



10868

	MOUSE ED50/AD50				IN VITRO		MONKEY
NIH #	H P	PPQ	T F	T F A	RBH (nM)	VD (nM)	SDS
10815	I [b]	3.8[b]	I [b]	I [b]	>6000[c,d]	6.4(100%)[A][c,e]	NS (3,15)[c,f]
10854	I	I	I	I	BIND[g]	515(46%)[NA]	NS
10868	I	0.01	0.4	I			P S[h]

a) See text for explanation of column headings and abbreviations.

b) Previously reported - 1995.

c) Previously reported - 1994.

d) BIND: μ=488, δ= 0.9, κ=1170 nM.

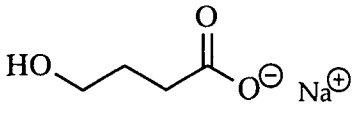
e) Relatively selective δ-agonist.

f) No exacerbation of withdrawal, ataxia, slowing; perhaps non-opioid.

g) BIND: μ=>6000, δ= >6000, κ=>6000 nM.

h) Fewer behavioral effects observed than with clonidine.

TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD#	SA[a]	DD[b]
0044	Did not maintain behavior. No reinforcing effect.	PB-trained monkeys: No[c] AMPH-trained monkeys: 50%[d,e]

a) Self-administration (monkey).
b) Drug discrimination (intragastric administration, monkey).
c) No drug-appropriate responding in PB-trained monkeys.
d) Maximum of 50% drug-appropriate responding in AMPH-trained monkeys. The response was not dose-related.
e) The drug may have weak AMPH-like subjective effects, but probably no PB-like subjective effects in humans.

DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (1996)

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All compounds, except the classical opioid agonist and antagonist subtypes and I-PP that were known to us, were supplied by Dr. Arthur Jacobson, Laboratory of Medicinal Chemistry, NIDDK, NIH. These studies were conducted under the auspices of the Drug Evaluation Committee of the College on Problems of Drug Dependence. See summary of new data in Table 1.

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 sterile water for injection. 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 2.

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.

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. SUMMARY OF NEW DATA

Compound NIH Number	Chemical Name or Generic Class	MOUSE					RAT		MONKEY		
		TF	TFvsM	PPQ	HP	PA_2	SM	PPD	SDS	PPT-W	PPD
0001	Morphine sulfate	T[a]		T[a]							
4591	Dextrorphan Tartrate							T			
7890	Naloxone	T[a]									
8503	Naltrexone	T[a]									
10322	14-Hydroxydihydromorphinone	T[a]									
10533	Cyclohexylpyrrolidine (U-50,488)	T[a]									
10588	Binaltorphamine (nor BNI)	T[a]	T[a]								
10589	Naltrindole (NTI)	T[a]	T[a]								
10590	Methyl Naltrindole	T[a]									
10672	4-Benzofuranacetamide	T[a]	T[a]								
10797	Codeine-6-O-sulfate	T	T	T	T	-	-	-	T	-	-
10798	Morphine-6-O-sulfate	T	T	T	T	-	-	-	T	-	-
10806	Buprenorphine-3-O-ether	T	T	T	T	-	-	-	T	-	-
10807	Diprenorphine-3-O-ether	T	T	T	T	-	-	-	T	-	-
10808	Naltrexone-3-O-ether	T	T	T	T	-	-	-	T	-	-
10815	N,N-Diethylbenzamide	T									
10834	4-Phenylpiperidine	T	T	T	T	-	-	-	T	-	-
10835	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10836	(+)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10842	Oxymorphindole	T	T	T	T	-	-	-	T	-	-
10844	14-Amido-dihydromorphinone	T[b]	T	T	T	-	-	-	T	-	-
10845	14-Amido-dihydromorphinone	T[b]	T	T	T	-	-	-	T	-	-
10847	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10848	(+-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10849	14-Amido-dihydromorphinone	T	T	T	T	-	-	-	T	-	-
10852	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10853	(+)-6,7-Benzomorphan	T	T	T	T		-	-	T	-	-

Table 1. SUMMARY OF NEW DATA (Continued)

Compound NIH Number	Chemical Name or Generic Class	MOUSE					RAT		MONKEY		
		TF	TFvsM	PPQ	HP	PA_2	SM	PPD	SDS	PPT-W	PPD
10854	Pyrimidinyl-piperazine	T	T	T	T	-	-	-	T	-	-
10855	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10856	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10857	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10858	(-)-6,7-Benzomorphan										
10862	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10863	(-)-6,7-Benzomorphan	T [c]	T	T	T	-	-	-	T	-	-
10864	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10865	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10866	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10868	Lofexidine	T [d]	T	T	T	-	-	-	T	-	-
10869	(-)-6,7-Benzomorphan	T	T	T	T	-	-	-	T	-	-
10872	(+)-6,7-Benzomorphan	T		T	T		-	-	-	-	-
10873	4-Phenylpiperazine	T	T	T	T	-	-	-	T	-	-
10891	Peptide (DAMGO)	T [e]									
10892	Peptide (DPDPE)	T [e]	T [e]								
10893	Peptide (ICI 174,864)	T [e]									
10894	Naloxonazine	T [e]									

T = tests performed.

[a,e]Special evaluation of agonist and antagonist subtypes in mouse T. F. and PPQ models. [b]Special time-course study in mouse T. F. test. [c]Special naloxone vs NIH 10863 in T. F and PPQ tests. [d]Special naloxone AD50 vs ED80 of NIH 10868 in T. F. test.

Table 2

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick	Tail-Flick Antagonist	Phenylquinone	Hot-Plate
Pentazocine	15% at 10.0	18 (12-26)	1.7 (1.0-2.5)	13% at 30.0
Cyclazocine	17% at 1.0[a]	0.03 (0.02-0.78)	0.01 (0.005-0.03)	25% at 9.0
Nalorphine•HCl	None at 10.0	2.6 (0.7-1.0)	0.6 (0.03-1.44)	13% at 30.0
Naloxone•HCl	None at 10.0	0.04 (0.0-0.09)	No Activity	----
Naltrexone•HCl	None at 10.0	0.007 (.002-0.02)	No Activity	----
Morphine•SO_4	1.92 (0.89-4.14)	Inactive	0.4[b] (0.2-0.8)	0.85 (0.39-1.86)
Codeine•PO_4	----	Inactive	8.25 (5.12-13.29)	6.4 (2.4-6.8)
Meperidine•HCl	8.37 (4.58-15.27)	Inactive	----	4.6

[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 pA_2 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-1) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x-l) were plotted. The pA_2 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 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) NalmefeneMorphine	8.0 (7.6 - 8.3)-1-1	8.0 (7.7 - 7.6)
3) NaltrexoneMorphine	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)-l-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 uni y, 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.

Special Intracerebroventricular Tail-Flick and PPQ Assays. In order to develop an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ tests and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to accomodate the fact that no delta agonist is available which is active by peripheral routes of administration. These special data are summarized in Tables 4-9.

TABLE 4. Effects of opioid agonists subtypes in mouse T. F. test.

	Antagonist (s.c. or i.c.v)	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v)	Agonist Pretreatment Time	ED_{50} or AD_{50} (95% Confidence Limits)
			Morphine•SO_4(i.c.v) mu agonist	10 m	ED_{50}=0.3 (0.10 to 0.90) µg/brain Slope - 1.37
			NIH 10672 (i.c.v) kappa agonist	10 m	ED_{50}=0.03 (0.08 to 0.090) µg/brain Slope - 1.50
			NIH 10533 (i.c.v) kappa agonist	10 m	ED_{50}=7.2 (3.10 to 16.45) µg/brain Slope - 2.20
			DPDPE (i.c.v) delta agonist	10 m	ED50=1.85 (0.18 to 5.93) µg/brain Slope - 2.22
			NIH 10815 (i.c.v) delta agonist	10 m	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 (i.c.v) delta agonist	1 h	5 µg/brain: 0% m.p.e. 1.5 µg/brain: 21% m.p.e. 0.5 µg/brain: 8% m.p.e.
			DAMGO (i.c.v) 0.005, 0.015 and 0.05 µg/brain mu agonist	20 m	ED50=0.015 (0.005 - 0.045) µg/brain µg/brain Slope - 2.56

Comment: All of the opioid agonist subtypes except the delta agonist NIH 10815 were active in the tail-flick test when given i.c.v. NIH 10672 and DAMGO showed remarkable potency.

TABLE 5. Effects of kappa antagonist (nor BNI) vs opioid agonist subtypes in mouse T.F. and PPQ assays.

	Antagonist (s.c. or i.c.v.) Nor-BNI (kappa antagonist)	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v.)	Agonist Pretreatment Time	ED_{50} or AD_{50} (95% Confidence Limits)
	NIH 10588 (s.c.) 1,3 and 10 mg/kg	2 h	TF Test MSO_4 ED80 (i.c.v.) 1.5 µg/brain (mu agonist)	10 m	30 mg/kg: 1% antagonism 10 mg/kg: 1% antagonism 1 mg/kg: 8% antagonism
	NIH 10588 (s.c.) 0.3, 1 and 3 mg/kg	2 h	TF Test NIH 10533 ED_{80} (i.c.v.) 30 µg/brain (kappa agonist)	10 m	AD_{50} = 1.45 (0.82 to 2.58) mg/kg Slope - 3.18
	NIH 10588 (s.c.) 0.3, 1,3 and 10 mg/kg	2 h	TF Test NIH 10672 - ED_{80} (i.c.v.) 0.15 µg/brain (kappa agonist)	10 m	AD_{50} = 1.92 (0.60 to 6.12) mg/kg Slope - 1.50
	NIH 10588 (i.c.v.) 1, 10 and 30 µg/brain	2 h	TF Test NIH 10672 ED_{80} (s.c.) 0.1 mg/kg (kappa agonist)	20 m	AD_{50} = 0.86 (0.32 to 2.32) µg/brain Slope - 1.84
	NIH 10588 (s.c.) 1, 10 and 30 mg/kg	2 h	TF Test DPDPE ED_{80} (i.c.v.) 5 µg/brain	10 m	30 mg/kg: 15% antagonism 10 mg/kg: 3% antagonism 1 mg/kg: 0% antagonism
	NIH 10588 (i.c.v.) 0.5, 1.5 and 5.0 µg/brain	2 h	PPQ Test DPDPE ED_{80} (i.c.v.) 1.5 µg/brain	10 m	AD_{50} = 2.15 (0.88 - 5.23) µg/brain Slope = 2.06
	NIH 10588 (s.c.) 1,3 and 10 mg/kg	2 h	PPQ Test DPDPE ED_{80} (i.c.v.) 1.5 µg/brain	10 m	AD_{50} = 5.0 (2.76 to 9.05) mg/kg Slope - 3.08

Comment: Under conditions of this test, nor BNI was highly selective in blocking the effects of kappa agonists in the T. F. test. Selectivity in the PPQ test was not demonstrated vs DPDPE.

TABLE 6. Effect of opioid agonists subtypes vs ß-FNA in T.F. test

	Antagonist (s.c. or i.c.v.) ß-FNA - mu antagonist	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v.)	Agonist Pretreatment	ED_{50} or AD_{50} (95% Confidence Limits)
	ß-FNA (i.c.v.) 1,5 and 10 µg/brain	4 h	MSO_4 ED_{80} (i.c.v.) 1.5 µg/brain	20 m	AD50 = 4.22 (1.37 to 13.02) µg/brain Slope - 1.33
	ß-FNA (i.c.v.) 1,5 and 10 µg/brain	4 h	NIH 10672 ED_{80} (s.c.) 0.1 mg/kg	20 m	10 µg/brain: 5 % antagonism
	ß-FNA (i.c.v.) 1,5 and 10 µg/brain	4 h	DPDPE ED_{80} (i.c.v.) 5 µg/brain	20 m	10 µg/brain: 59 % antagonism
	ß-FNA (i.c.v.) 1.5 and 10 µg/brain	24h	MSO_4 ED_{80} (i.c.v.) 1.5 µg/brain	10 m	10 µg/brain: 49% antagonism 5 µg/brain : 56% antagonism 1 µg/brain : 24% antagonism
	ß-FNA (i.c.v.) 1,5 and 10 µg/brain	24h	MSO_4 ED_{80} (s.c.) 4 mg/kg	20 m	10 µg/brain: 87% antagonism 5 µg/brain : 8 1% antagonism 1 µg/brain : 74% antagonism
	ß-FNA (i.c.v.) 1,5 and 10 µg/brain	24h	NIH 10672 ED_{80} (i.c.v.) 0.15 µg/brain	10 m	12 µg/brain: 10% antagonism
	ß-FNA (i.c.v.) 1,5 and 10 µg/brain	24h	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	20 m	12 µg/brain: 46% antagonism
	ß-FNA (i.c.v.) 1,5 and 10 µg/brain	24h	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	10 m	10 µg/brain: 10% antagonism

Comment: ß-FNA (i.c.v.) given 4 h prior to testing-selectively antagonized morphine·SO_4 (i.c.v.). However, 24-h pretreatment with ß-FNA did not produce remarkable antagonism vs any of the opioid agonists..

TABLE 7. Effect of Naloxonazine, the selective mu_1 and mu_2 antagonist, on opioid agonist subtypes in the T. F. test.

	Antagonist (s.c. or i.c.v). Naloxonazine (mu antagonist)	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v.)	Agonist Pretreatment Time	ED_{50} of AD_{50} (95% Confidence Limits)
	Naloxonazine (s.c.) 0.03, 0.1 and 0.3 mg/kg	30 m	MSO_4 ED_{50} (s.c.) 5 mg/kg (mu agonist)	10 m	AD_{50} = 0.06 (0.03 to 0.1) mg/kg Slope - 3.09
	Naloxonazine (s.c.) 0.3, 1 and 3 mg/kg	30 m	NIH 10672 ED_{80} (s.c.) 0.1 mg/kg (kappa agonist)	10 m	AD_{50} = 0.98 (0.36 to 2.7 1) mg/kg Slope - 1.47
	Naloxonazine (s.c.) 0.1, 0.3 and 1 mg/kg	30 m	MSO_4 ED_{80} (i.c.v.) 1.5 µg/brain (mu agonist)	10 m	AD_{50} = 0.27 (0.09 to 0.78) mg/kg Slope - 2.42
	Naloxonazine (s.c.) 0.1, 0.3 and 1 mg/kg	30 m	MSO_4 ED_{80} (i.c.v.) 1.5 µg/brain (mu agonist)	10 m	AD_{50} = 0.26 (0.11 to 0.61) mg/kg Slope - 2.18
	Naloxonazine (s.c.) 0.01, 0.03 and 0.1 mg/kg	30 m	NIH 10672 ED_{80} (i.c.v.) 0.15 µg/brain (kappa agonist)	10 m	AD_{50} = 0.05 (0.02 to 0.1) mg/kg Slope - 2.54
	Naloxonazine (s.c.) 0.03, 0. 1 or 0.3 mg/kg	30 m	NIH 10672 ED_{80} (i.c.v.) 5.0 µg/brain (kappa agonist)	10 m	AD_{50} = 0.08 (0.03 to 0.22) mg/kg Slope - 1.75
	Naloxonazine (s.c.) 0.03, 0. 1 or 0.3 mg/kg	30 m	DPDPE ED_{80} (i.c.v.) 5.0 µg/brain (delta agonist)	10 m	AD_{50} = 0.1 (0.04 to 0.26) mg/kg Slope - 1.87
	Naloxonazine (s.c.) 0.01, 0.03, 0.1 or 0.3 mg/kg	30 m	DPDPE ED_{80} (i.c.v. 5.0 µg/bra.in (delta agonist)	10 m	AD_{50} = 0.06 (0.02 to 0.15) mg/kg Slope - 1.97

Comment: Naloxonazine given s.c. showed greater selectivity for delta (DPDPE) i.c.v. and kappa (NIH 10672) i.c.v. agonists than the mu (morphine) i.c.v. agonist. Greater selectivity for morphine (s.c.) compared to NIH 10672 (s.c.) was demonstrated when the agonist was given s.c.

TABLE 8. Effect of delta antagonists naltrindole and ICI 174864 on opioid agonist subtypes in the T. F. and PPQ tests.

	Antagonist (s.c. or i.c.v.) delta antagonist	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v.)	Agonist Pretreatment Time	ED_{50} or AD_{50} (95% Confidence Limits)
	NIH 10589 (i.c.v.) (Naltrindole) 10, 20 and 30 µg/brain	10 m	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	10 m	AD_{50}=19.64 (12.47 to 30.90) µg/brain Slope - 4.04
	NIH 10589 (i.c.v.) (Naltrindole) 1, 10 and 30 µg/brain	20 m	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	10 m	30 mg/kg: 0% antagonism 10 mg/kg: 4% antagonism 1 mg/kg: 8% antagonism
	NIH 10589 (s.c.) (Naltrindole) 1, 10 and 30 mg/brain	20 m	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	10 m	30 mg/kg: 0% antagonism 10 mg/kg: 20% antagonism 1 mg/kg: 3% antagonism
	NIH 10589 (s.c.) (Naltrindole) 1, 10 and 30 mg/brain	2 h	NIH 10533 ED_{80} (i.c.v.) 30 µg/brain (kappa agonist)	10 m	30 mg/kg: 15% antagonism 10 mg/kg: 0% antagonism 1 mg/kg: 3% antagonism
	NIH 10589 (s.c.) (Naltrindole) 1,10 and 30 mg/kg	2 h	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	10 m	30 mg/kg : 4% antagonism 10 mg/kg : 8% antagonism 1 mg/kg : 15% antagonistm
	NIH 10590 (s.c.) (Methyl naltrindole) 1,10 and 30 mg/kg	20 m	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	10 m	30 mg/kg : 5% antagonism 10 mg/kg : 3% antagonism 1 mg/kg : 0% antagonistm
	ICI 174864 (i.c.v.) 1 and 3 µg/brain	20 m	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	10 m	3 µg/brain : 33% antagonism 1 µg/brain : 19% antagonism
	ICI 174864 (i.c.v.) 1,10 and 30 µg/brain	20 m	DPDPE ED_{80} (i.c.v 5 µg//brain (delta agonist)	10 m	30 µg/brain : 10% antagonism 10 µg/brain : 4% antagonism 1 µg/brain - 13% antagonism

TABLE 9. Interaction of DAMGO, a mu agonist, with opioid antagonist subtypes in the mouse T. F. test.

	Antagonist (s.c. or i.c.v). delta antagonist	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v.)	Agonist Pretreatment Time	ED_{50} of AD_{50} (95% Confidence Limits)
	-FNA (i.c.v.) 1,5 and 10 µg/brain	4 h	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	AD_{50} = 3.85 (1.59 - 9.35) µg/brain Slope - 1.69
	NIH 10589 (s.c.) (Naltrindole) 1,10 and 30 mg/kg	30 m	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	30 mg/kg: 10% antagonism 10 mg/kg: 15% antagonism 1 mg/kg: 4% antagonism
	NIH 10588 (s.c.) (Nor-BNI) 1,10 and 30 mg/kg	2 h	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	30 mg/kg: 7% antagonism 10 mg/kg: 8% antagonism 1 mg/kg: 11% antagonism
	Naloxone (s.c.) 0.1, 0.3, 1 and 3 mg/kg	30 m	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	AD_{50} = 0.45 (0.17 - 1.16) µg/brain Slope - 1.92

Comment: DAMGO interacts with mu but not kappa or delta antagonists.

TABLE 8. Effect of delta antagonists naltrindole and ICI 174864 on opioid agonist subtypes in the T. F. and PPQ tests. (Continued)

	Antagonist (s.c. or i.c.v). delta antagonist	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v.)	Agonist Pretreatment Time	ED_{50} or AD_{50} (95% Confidence Limits)
	ICI 174864 (i.c.v.) 0.3, 1 and 3 µg/brain	20 m	DPDPE ED_{80} (i.c.v.) 5 µg/brain (delta agonist)	20 m	3 µg/brain : 0% antagonism 1 µg/brain : 0% antagonism
	NIH 10589 (s.c.) (Naltrindole) 1,10 and 30 mg/kg	20 m	TF Test MSO_4 ED_{80} (i.c.v.) 0.15 µg/brain (mu agonist)	10 m	30 mg/kg: 1% antagonism 10 mg/kg: 1% antagonism 1 mg/kg: 6% antagonism
	NIH 10589 (s.c.) (Naltrindole) 0.1, 0.3 and 1 mg/kg	20 m	PPQ Test MSO_4 ED_{80} (i.c.v.) 1.5 µg/brain (mu agonist)	10 m	AD_{50} = 0.44 (0.22 to 0.87) mg/kg Slope - 2.66
	NIH 10589 (i.c.v.) (Naltrindole) 0.15, 0.5, 1.5 and 5 µg/brain	10 m	PPQ Test DPDPE ED_{80} (i.c.v.) 1.5 µg/brain (delta agonist)	10 m	AD_{50} = 1.38 (0.41 to 4.68) µg/brain Slope - 1.06
	NIH 10589 (s.c.) (Naltrindole) 1, 10 and 30 mg/kg	20 m	PPQ Test DPDPE ED_{80} (i.c.v.) 1.5 µg/brain (delta agonist)	10 m	AD_{50} = 0.13 (0.1 to 0.27) mg/kg Slope - 2.03
	NIH 10589 (s.c.) (Naltrindole) 1, 10 and 30 mg/kg	20 m	PPQ Test NIH 10672 ED_{80} (i.c.v) 0.15 µg/brain (kappa agonist)	10 m	30 mg/kg : 50% antagonism 10 mg/kg : 33% antagonism 1 mg/kg : 0% antagonism

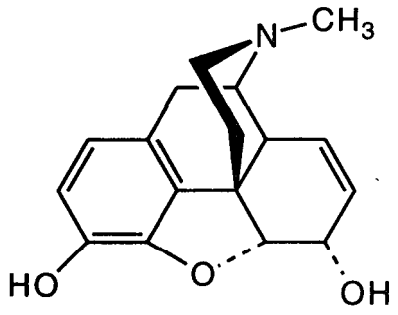
Comment: Naltrindole (i.c.v.) antagonized DPDPE (i.c.v.) antinociception only when given concomitantly with the agonist in the T. F. test. ICI 174864 and methyl naltrindole (NIH 10590) (i.c.v.) were inactive vs DPDPE when given 20 m before testing. In the PPQ test, naltrindole displayed more selectivity for the delta agonist than for the mu or kappa agonists.

TABLE 9. Interaction of DAMGO, a mu agonist, with opioid antagonist subtypes in the mouse T. F. test.

	Antagonist (s.c. or i.c.v.) delta antagonist	Antagonist Pretreatment Time	Agonist (s.c. or i.c.v.)	Agonist Pretreatment Time	ED_{50} or AD_{50} (95% Confidence Limits)
	ß-FNA (i.c.v.) 1, 5 and 10 µg/brain	4 h	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	AD50=3.85 (1.59 - 9.35) µg/brain Slope - 1.69
	NIH 10589 (s.c.) (Naltrindole) 1, 10 and 30 µg/brain	30 m	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	30 mg/kg: 10% antagonism 10 mg/kg: 15% antagonism 1 mg/kg: 4% antagonism
	NIH 10588(s.c.) (Nor-BNI) 1, 10 and 30 mg/kg	2 h	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	30 mg/kg: 7% antagonism 10 mg/kg: 8% antagonism 1 mg/kg: 11% antagonism
	Naloxone (s.c.) 0.1, 0.3, 1 and 3 mg/kg	30 m	DAMGO ED_{80} (i.c.v.) 0.05 µg/brain	20 m	AD_{50} = 0.45 (0.17 - 1.16) µg/brain Slope - 1.92

Comment: DAMGO interacts with mu but not kappa or delta antagonists.

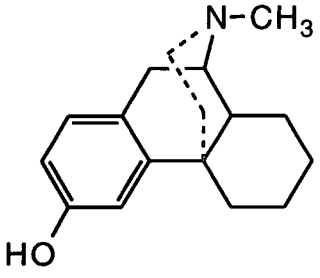
NIH 0001 Morphine



SPECIAL MOUSE DATA[a]

[a]See TABLES 4, 5, 6, 7 and 8

NIH 04591 (+)-3-Hydroxy-N-methylmorphinan tartrate or Dextrorphan Tartrate



MOUSE DATA - ED50 OR AD50
mg/kg (95% C.L.) or % change

1) TF - Inactive at 1.0, 10.0 and 30.0[a]
2) TF vs. M - 13% at 10.0, 30% at 30.0[a] and 61% at 100.0
3) PPQ - 23.8 (12.3 - 46.0)[a,b]
4) HP - Approx 30.0[a]

[a]Published previously (NIDA Monog. 67, 1986)
[b]At 0.1 and 1.0 mg/kg naloxone partly antagonized this effect

MONKEY - Monkey data reported previously in NIDA Monog. 67, 1986.

A. SDS

Dextrorphan reduced the total number of withdrawal signs but at 4.0 mg/kg, it produced severe ataxia, slowing, body sag and partial eyelid ptosis. Dose range studied was 0.25 - 4.0 mg/kg s.c.

B. PPt-W

At doses of 1.0 and 4.0 mg/kg dextrorphan did not precipitate withdrawal. Dose-related side-effects as indicated above.

C. PPD

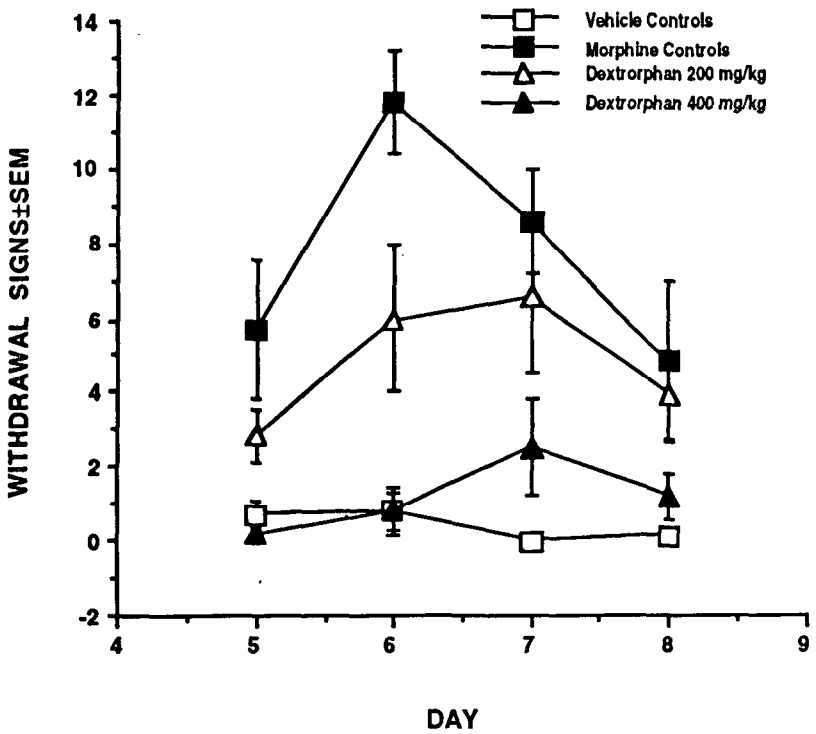
Given 4-6 times a day for 30 days at doses ranging from 3.0 to 13.0 mg/kg, dextrorphan produced withdrawal phenomena. Tolerance to the acute effects developed rapidly up to a dose of 10.0 mg/kg. When the monkeys were placed in abrupt withdrawal, a syndrome characterized by the signs lying on side or abdomen, scratching, wet-dog shakes, fighting, pacing, frequent touching of genital area, and rubbing face against pen wall was observed. When the monkeys were challenged with naltrexone (1.0 mg/kg s.c.) withdrawal was

exacerbated. However, none of the monkeys ever showed rigid abdominal muscles or vocalized when their abdomens were palpated. These signs are considered important and distinguished morphine withdrawal from dextrorphan withdrawal in the monkey.

RAT DATA - Reported previously in NIDA Monog. 152, 1994.
(A) SM

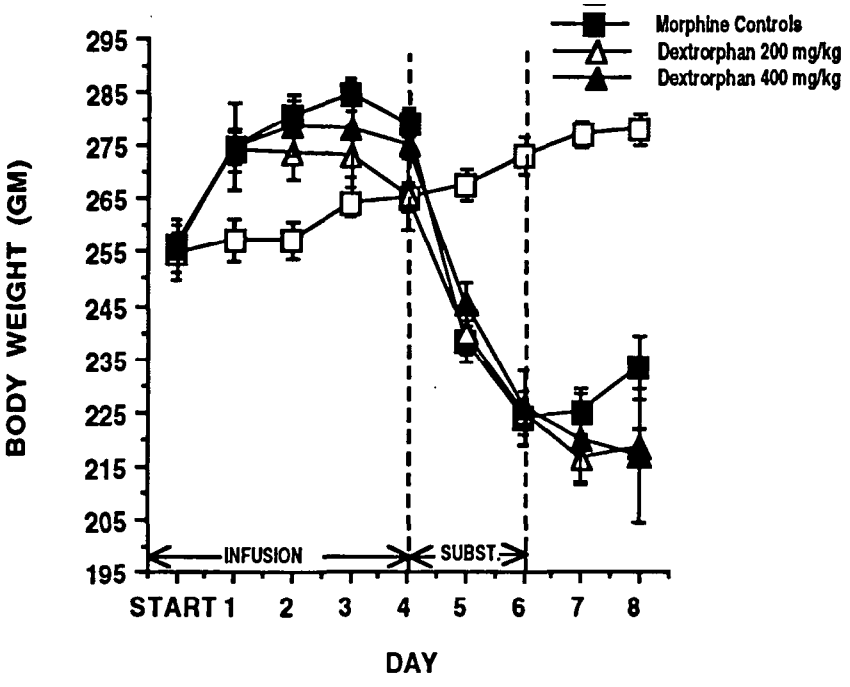
Unanesthetized, male, Sprague-Dawley rats previously fitted with intraperitoneal cannulas (Teiger, JPET, 1974) were made maximally dependent by continuously administered morphine using the following dose regimen: 50 mg/kg, day 1; 100 mg/kg, day 2 and 200 mg/kg, days 3 and 4. At the end of day 4, morphine was abruptly withdrawn and dextrorphan (200 or 400 mg/kg per day) or vehicle (8 ml per day) was substituted for morphine. A dose-related reduction in behavioral withdrawal signs was observed in rats receiving dextrorphan (see Fig. 1). The morphine-dependent rats given vehicle displayed the usual full complement of behavioral withdrawal signs. These behavioral signs were designated hypersensitivity, squeaking, aggression, wet-dog shakes, rubbing and chewing. None of the vehicle controls showed any withdrawal signs. However, the precipitous loss of body weight which occurred in the rats receiving morphine and vehicle or morphine and dextrorphan indicated that dextrorphan had no influence on this particular physiological withdrawal parameter (see Fig. 2). The results suggest that dextrorphan may selectively alter the behavioral expression of opioid dependence.

Figure 1. DEXTRORPHAN SM IN RAT INFUSION



NIH 04591 (Continued)

Figure 2. DEXTRORPHAN SM IN RAT INFUSION



RAT DATA - (New data)
(B) PPD

As shown in figure 3, Dextrorphan PPD in Rat Infusion, rats receiving 200 and 400 mg/kg showed dose-related abstinence signs when dextrorphan was abruptly withdrawn (See SM studies above). However, this withdrawal syndrome differed from that noted with morphine in one important respect, namely, body weight loss, figure 4 - Dextrorphan PPD in Rat Infusion. Dextrorphan produced mimimal loss of body weight.

Figure 3. DEXTRORPHAN PPD IN RAT INFUSION

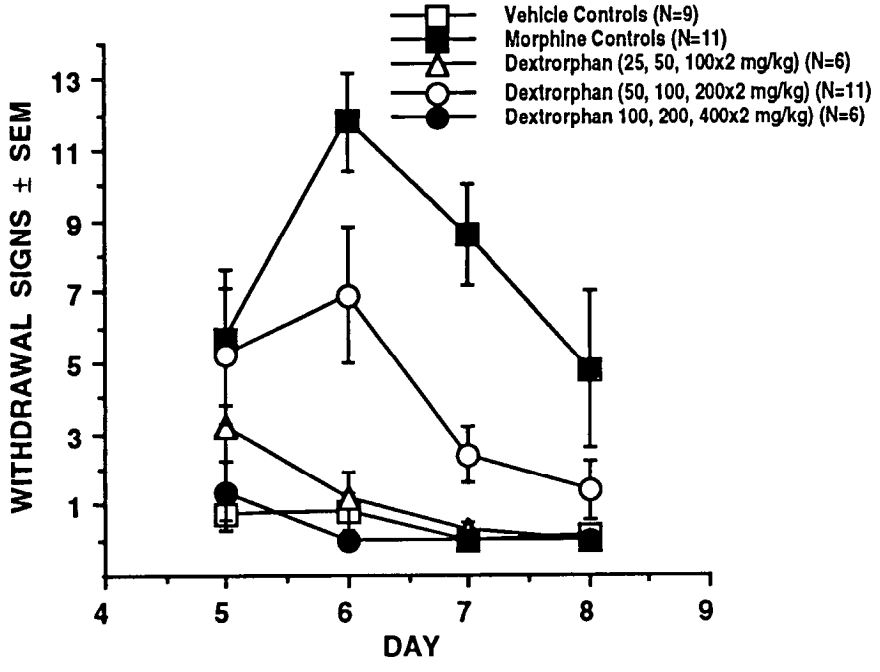
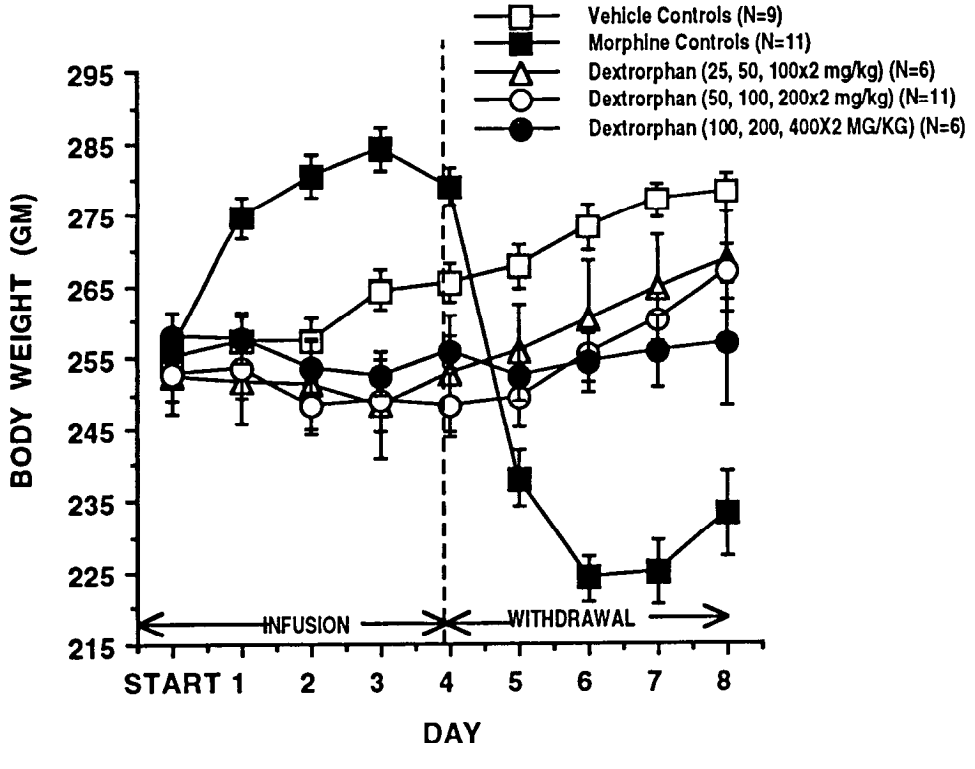


Figure 4. DEXTRORPHAN PPD IN RAT INFUSION

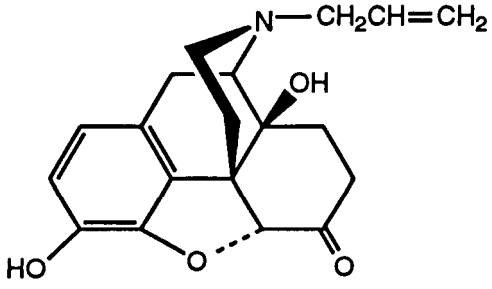


NIH 04591 (cont.)

Comment:

Dextrorphan produces physical dependence in rats and monkeys. In some respects, the abstinence syndromes are not unlike that observed with morphine. However, in the rat, weight loss is not observed and in the monkey, the abstinence sign designated rigid abdominal muscles and vocalization when abdomen palpated are not evident. These signs are considered pathognomonic for opioid physical dependence and distinguish morphine from dextrorphan withdrawal. Taken together, the results suggest that dextrorphan may interact indirectly with the opioid system, perhaps via the NMDA (N-Methyl-D-Aspartate) system.

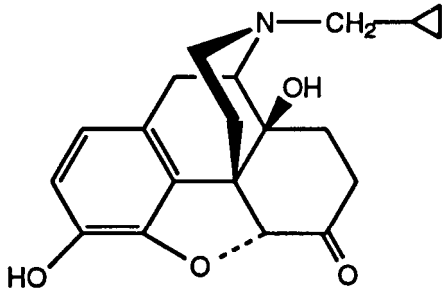
NIH 7890 Naloxone



SPECIAL MOUSE DATA

Clinical reports have been presented (Crain and Shen) that low doses of naloxone (NLX) (< 30 µg/kg) enhanced rather than attenuated analgesic effects of morphine or other agonists. We studied the effects of ultra-low doses of naloxone on antinociception in mice using using tail-flick assay. At doses of 0.05, 0.25, 0.5, 1.0 and 5.0 µg/brain and 0.1, 1.0, 10.0 and 100 µg/brain, NLX was ineffective. NLX at 0.5 µg/brain + morphine ED_{50} were ineffective and produced a 22% antagonism. Likewise, NLX at 1.0 ng/brain + morphine ED_{25} produced 73% antagonism.

NIH 8503 Naltrexone

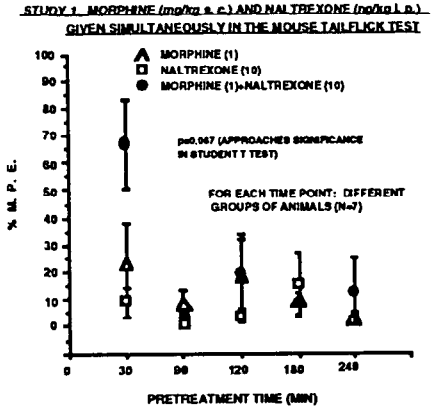


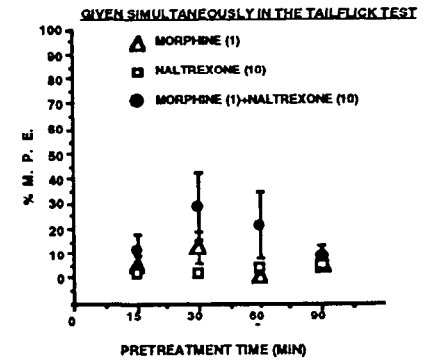
SPECIAL MOUSE DATA[a]

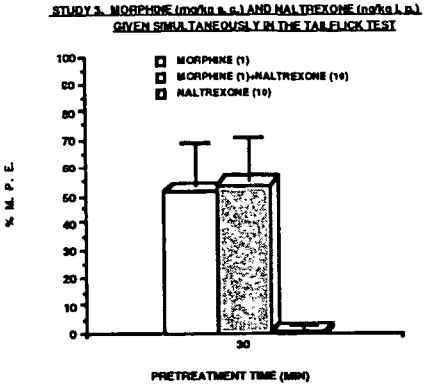
[a]See TABLE 10

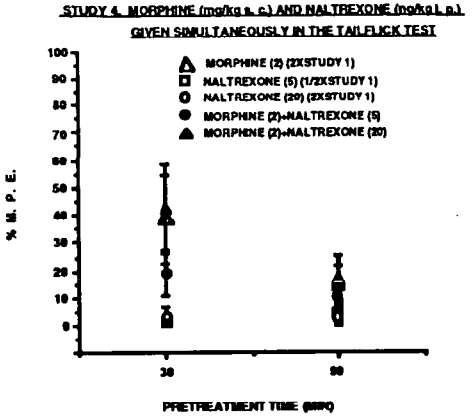
Comment: There is little evidence for the enhancement of morphine's antinociceptive effects with ultra-low doses of naltrexone (see Table 10).

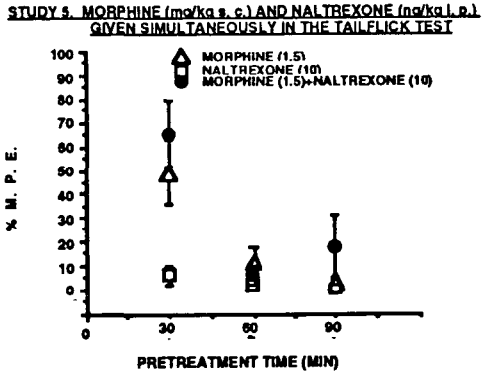
TABLE 10

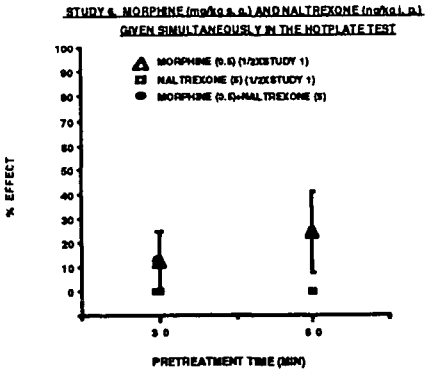

STUDY 1. MORPHINE (mg/kg s. c.) AND NALTREXONE (ng/kg i. p.)
GIVEN SIMULTANEOUSLY IN THE MOUSE TAILFLICK TEST
MORPHINE (1)
NALTREXONE (10)
MORPHINE (1)+NALTREXONE (10)
p=0.047 (APPROACHES SIGNIFICANCE IN STUDENT T TEST)
FOR EACH TIME POINT: DIFFERENT GROUPS OF ANIMALS (N=7)
% M. P. E.
PRETREATMENT TIME (MIN)


STUDY 2. MORPHINE (mg/kg s. c.) AND NALTREXONE (ng/kg i. p.)
GIVEN SIMULTANEOUSLY IN THE TAILFLICK TEST
MORPHINE (1)
NALTREXONE (10)
MORPHINE (1)+NALTREXONE (10)
% M. P. E.
PRETREATMENT TIME (MIN)

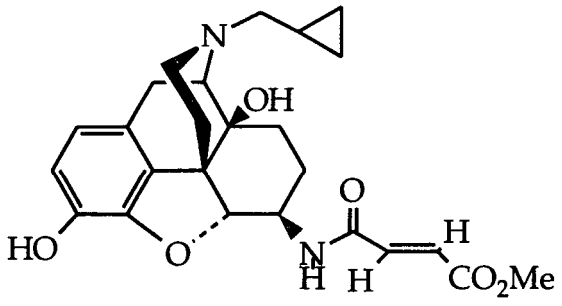

STUDY 3. MORPHINE (mg/kg s. c.) AND NALTREXONE (ng/kg i. p.)
GIVEN SIMULTANEOUSLY IN THE TAILFLICK TEST
MORPHINE (1)
MORPHINE (1)+NALTREXONE (10)
NALTREXONE (10)
% M. P. E.
PRETREATMENT TIME (MIN)


STUDY 4. MORPHINE (mg/kg s. c.) AND NALTREXONE (ng/kg i. p.)
GIVEN SIMULTANEOUSLY IN THE TAILFLICK TEST
MORPHINE (2) (2XSTUDY 1)
NALTREXONE (5) (1/2XSTUDY 1)
NALTREXONE (20) (2XSTUDY 1)
MORPHINE (2)+NALTREXONE (5)
MORPHINE (2)+NALTREXONE (20)
% M. P. E.
PRETREATMENT TIME (MIN)


STUDY 5. MORPHINE (mg/kg s. c.) AND NALTREXONE (ng/kg i. p.)
GIVEN SIMULTANEOUSLY IN THE TAILFLICK TEST
MORPHINE (1.5)
NALTREXONE (10)
MORPHINE (1.5)+NALTREXONE (10)
% M. P. E.
PRETREATMENT TIME (MIN)


STUDY 6. MORPHINE (mg/kg s. c.) AND NALTREXONE (ng/kg i. p.)
GIVEN SIMULTANEOUSLY IN THE HOTPLATE TEST
% EFFECT
PRETREATMENT TIME (MIN)

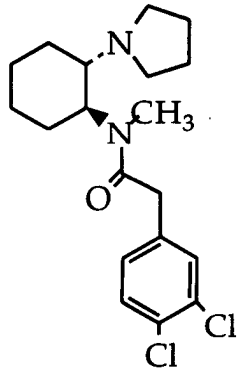
NIH 10323 ß-Funaltrexamine (ß-FNA)



SPECIAL MOUSE DATA[a]

[a]See TABLES 6 and 9

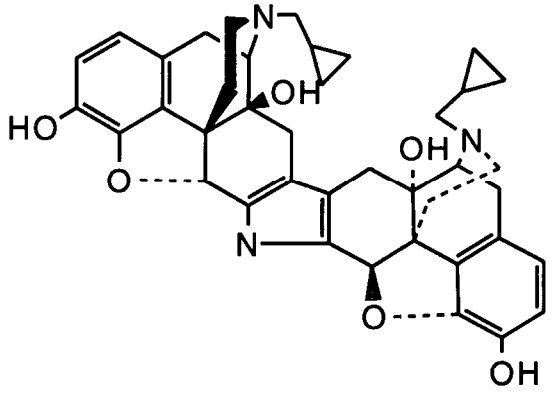
NIH 10533 (-)-*trans*-3,4-Dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzene-acetamide 1-tartrate [(-)-U50,488]



SPECIAL MOUSE DATA[a]

[a]See TABLES 4 and 5

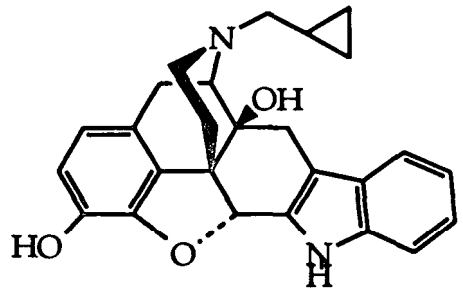
NIH 10588 Binaltorphimine (nor BNI)



SPECIAL MOUSE DATA[a]

[a]See TABLES 5 and 9

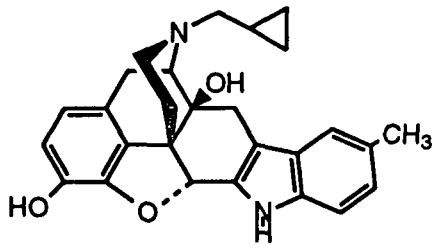
NIH 10589 Naltrindole (NTI)·HCl



SPECIAL MOUSE DATA[a]

[a]See TABLES 8 and 9

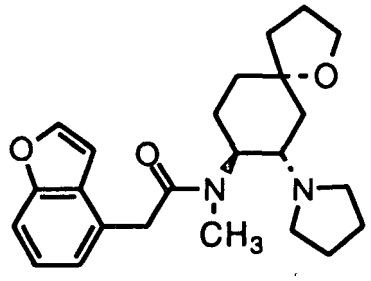
NIH 10590 Methyl Naltrindole•HCl



SPECIAL MOUSE DATA[a]

[a]See TABLE 8

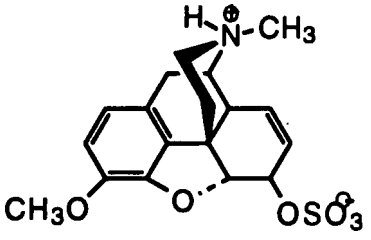
NIH 10672 (-)-[5R-(5α,8β)]-N-Methyl-N-7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]-4-benzofuranacetamide•HCl



SPECIAL MOUSE DATA[a]

[a]See TABLES 4, 5, 6, 7 and 8

NIH 10797 Codeine-6-O-sulfate zwitterion



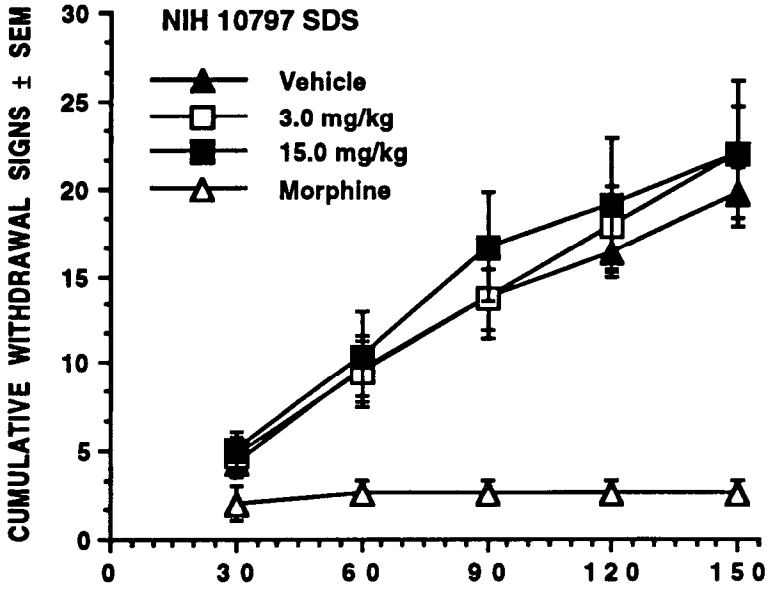
MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0 and 30.0[a]
TF vs M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 17% at 1.0, 23% at 10.0 and 43% at 30.0[a]
HP - 17% at 1.0, 25% at 10.0 and 38% at 30.0[a]

[a]35% hydroxypropyl-ß-cyclodextrin in water

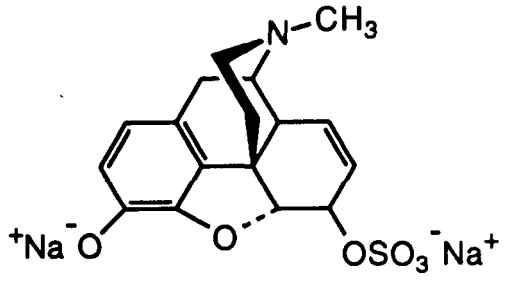
MONKEY DATA
(SDS)

At 3.0 and 15.0 mg/kg. NIH 10797 neither exacerbated withdrawal nor substituted for morphine (see fig.). Vehicles used were 10% and 20% DMSO aqueous solution, or 10% ethyl alcohol, 30% propylene glycol, 20% Tween 80 and H_2O.



Comment: NIH 10797 appears to be devoid of opioid activity.

NIH 10798 Morphine-6-O-sulfate disodium salt



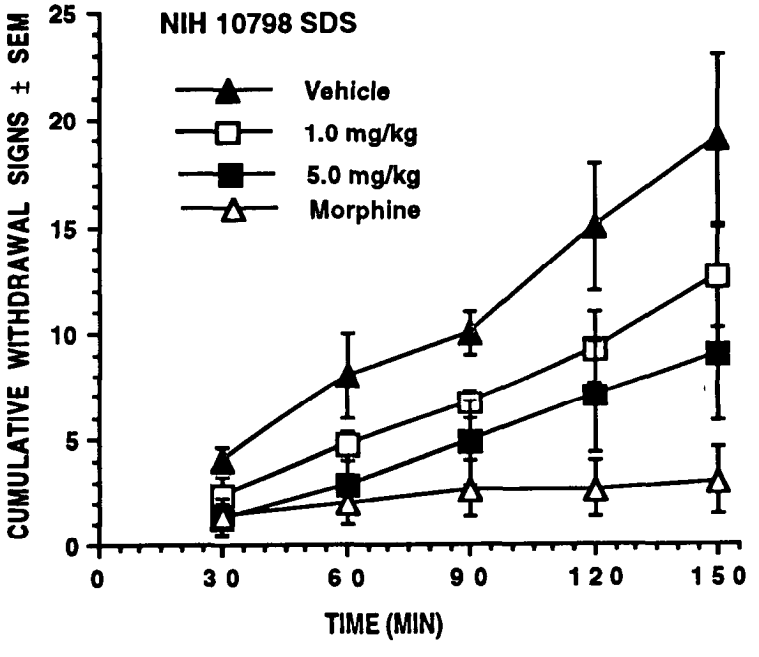
MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - 1.4 (0.6 - 3.5)[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - 0.3 (0.1 - 0.7)
HP - 0.4 (0.1 - 1.0)

[a]Slight ptosis, rapid breathing, moderate Straub tail and increased locomotor activity at 10.0 mg/kg.

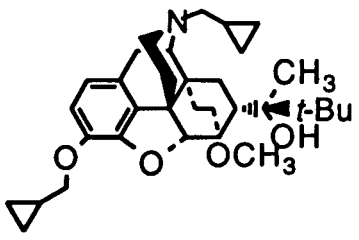
MONKEY DATA
(SDS)

NIH 10798 dose-dependently suppressed withdrawal in morphine-dependent monkeys (see fig.). Although the onset was rapid, duration of action was short, i.e., less than 90 m. Potency is approximately one-half that of morphine.



Comment: NIH 10798 appears to be a typical mu agonist.

NIH 10806 Buprenorphine-3-cyclopropylmethyl ether hydrochloride



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

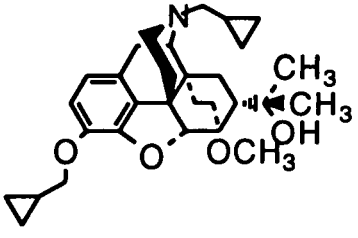
TF - 4% at 1.0, 8% at 10.0 and 50% at 30.0[a]
TF vs. M - 0% at 1.0, 10.0 and 30.0[a]
PPQ - 8.31 (4.12 - 16.80)[a]
HP 14.36 (5.22 - 39.50)[a]

[a]10% Tween 80 in water

MONKEY DATA
(SDS)

Drug supply was exhausted.

NIH 10807 Diprenorphine-3-cyclopropylmethyl ether hydrochloride



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

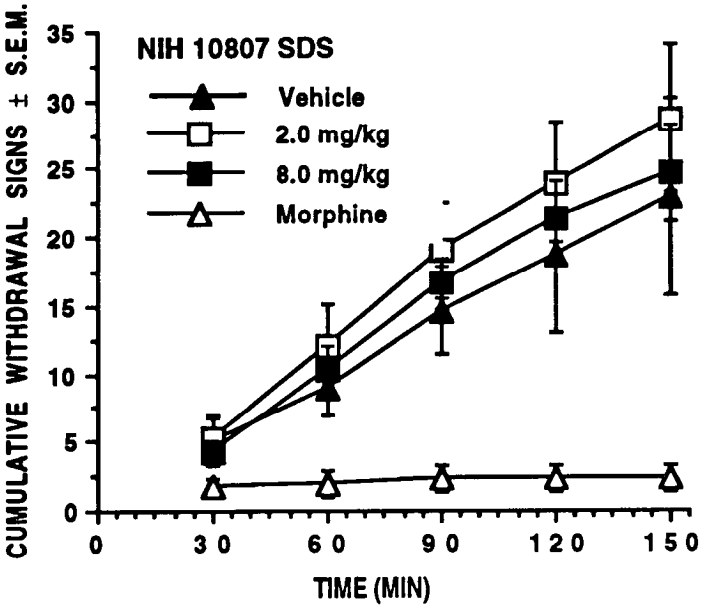
TF - 13% at 1.0, Inactive at 10.0 and 30.0[a]
TF vs. M - 0% at 1.0, 25% at 10.0 and 37% at 30.0[a]
PPQ - 6% at 1.0, 11% at 10.0 and 23% at 30.0
HP - Inactive at 1.0, 10.0 and 30.0

[a]15% hydroxypropyl ß-cyclodextrin aqueous solution

MONKEY DATA
(SDS)

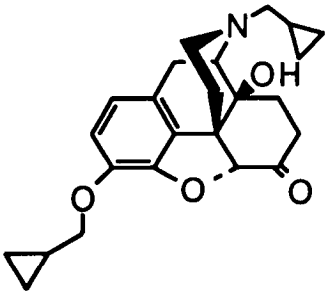
In the preliminary appraisal, the monkey was slow, ataxic, appeared disoriented and made clucking sounds and jerky movements. In the SDS test, NIH 10807 was evaluated at 2 and 8 mg/kg. The results are illustrated in the accompanying fig. A non dose-related rise in the number of withdrawal signs is evident. However, the data lacks statistical support. The side effects noted in the preliminary study were also observed in the SDS study. Vehicle was 25% hydroxypropyl-ß-cyclodextrin aqueous solution.

NIH 10807 (Continued)



Comment: NIH 10807 appears to have weak mu antagonist properties in monkeys. However, it produced pronounced overt behavioral effects.

NIH 10808 Naltrexone-3-cyclopropylmethyl ether hydrochloride



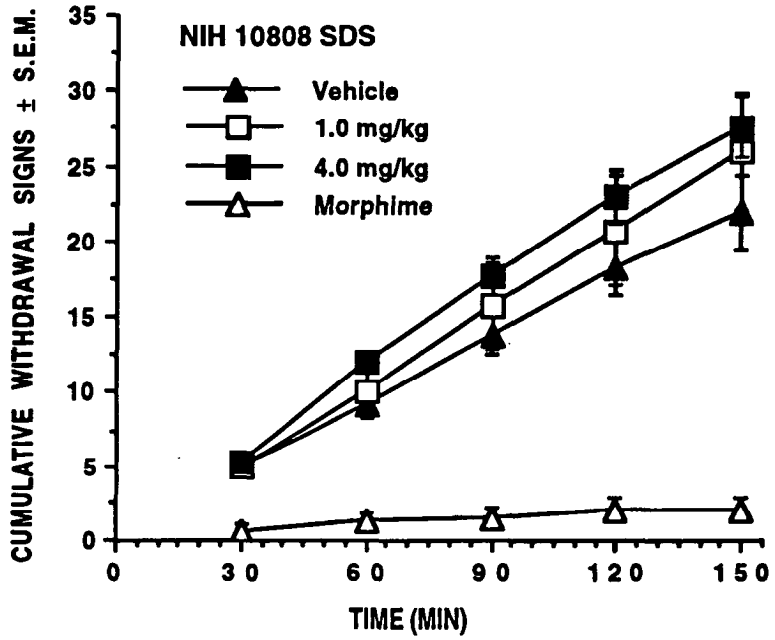
MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - 13% at 1.0, Inactive at 10.0 and 30.0
TF vs. M - 0.2 (0.1 - 0.4)
PPQ - 11% at 1.0, 9% at 10.0 and 40% at 30.0
HP - 13% at 1.0, 10.0 and 30.0

MONKEY DATA
(SDS)

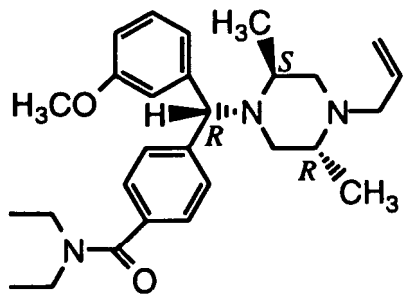
As shown in the fig., NIH 10808 did not substitute for morphine. The increased scores at 1 and 4 mg/kg suggest that this compound may have exacerbated withdrawal. However, statistical

treatment of the data (Kruskal/Wallis analyses of variance and post hoc Mann-Whitney U tests) did not reveal significant differences ($p < 0.05$) compared to vehicle.



Comment: The data suggest that NIH 10808 has weak mu antagonist-activity in mice and monkeys.

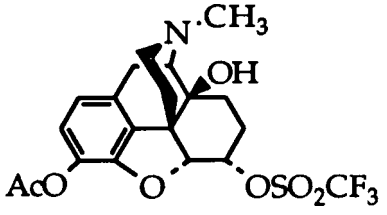
NIH 10815 (+)-4-[(R)-(2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-metoxybenzyl]-N,N-diethylbenzamide



SPECIAL MOUSE DATA[a]

[a]See TABLE 4.

NIH 10825 3-Acetoxy-6α-trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5α-epoxymorphinan



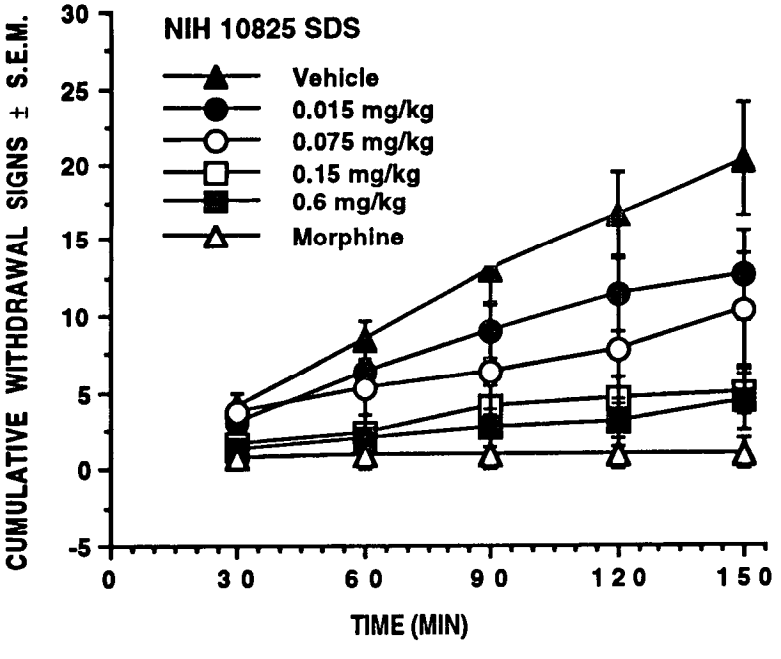
MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - 0.14 (0.05 - 0.39)[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 0.04 (0.02 - 0. 10)[a]
HP - 0.22 (0.08 - 0.58)[a,b]

[a]Vehicle - Lactic acid and water
[b]Straub tail and increased locomotion at 1.0

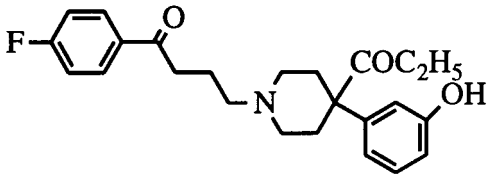
MONKEY DATA
(SDS)

As can be seen in the accompanying figure, NIH 10825 substituted completely for morphine in a dose-dependent manner at doses of 0.015, 0.075, 0.15 and 0.60 mg/kg. Onset of action was prompt and duration was at least 2 1/2 h. Potency estimate is 20 x that of morphine sulfate, the positive control. Vehicle was either dilute aquous lactic acid or 10% hydroxypropyl-ß-cyclodextrin in sterile water.



Comment: NIH 10825 appears to be a typical mu agonist.

NIH 10834 1-[3-Fluorobenzoyll-4-(3-hydroxyphenyl)-4-(1-oxypropyl)piperidine·HCl



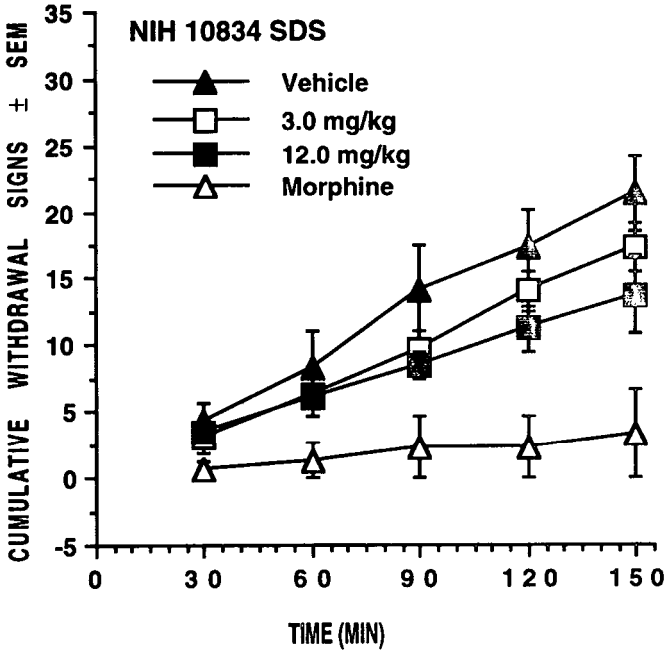
MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - 11% at 1.0, 40% at 10.0 and 23% at 30.0[a,b]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a,b]
PPQ - 0.48 (0.23 - 1.0)[a,c]
HP - 0% at 1.0 and 10.0, 13% at 30.0[a,c]

[a]Vehicle - 5% Hydroxypropyl ß-cyclodextrin in water
[b]Ptosis, immobility at 10.0 and 30.0
[c]Ptosis, immobility and lying flat on abdomen at 10.0 and 30.0

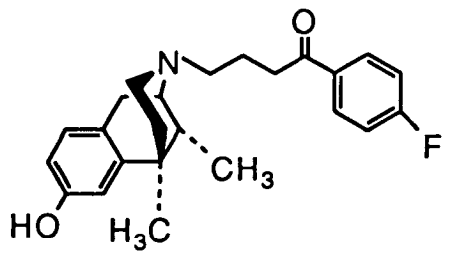
MONKEY DATA
(SDS)

The data shown in the figure suggest a modest dose-related attenuation of withdrawal. However, NIH 10834 neither substituted for morphine nor exacerbated withdrawal. The apparent attenuation was probably due to severe cataleptic effects of this drug, i.e., the animals sat motionless or assumed unusual positions for extended periods. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in water.



Comment: The data suggest neuroleptic-like activity for this compound.

NIH 10835 (-)-5,9α-Dimethyl-2-[3-(fluorobenzoyl)propyl]-2'hydroxy-6,7-benzomorphan•HC1



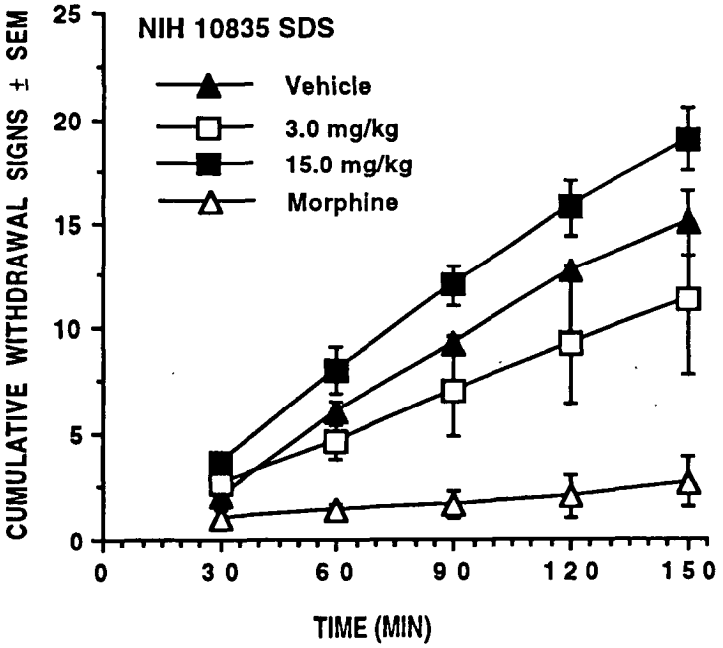
MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - 10.1 (4.4 - 22.6)[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 2.8 (1.1 - 7.1)[a]
HP - 0% at 1.0 and 10.0 and 25% at 30.0[a,b]

[a]5% hydroxypropyl- ß-cyclodextrin in water
[b]eyelid ptosis and reduced locomotion

MONKEY DATA
(SDS)

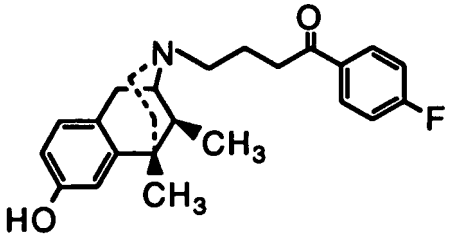
The vehicle controls performed poorly in this assay thereby obscuring the interpretation of the data. NIH 10835 may have attenuated withdrawal at the low dose but if it did, the effect was not dramatic (see fig.). At the high dose, the signs designated slowing, eyelid ptosis, body jerks, pale face, and disorientation were observed. Although the data in the fig. suggest antagonist properties, the behavioral profile is not consistent with this interpretation. Vehicle was 10% hydroxypropyl-ß-cyclodextrin.



NIH 10835 (Continued)

Comment: Antinociception was observed in the TF and PPQ assays as were behavioral effects. In the monkey, NIH 10835 apparently neither substituted for morphine or exacerbated withdrawal. The behavioral signs in both species suggest neuroleptic properties.

NIH 10836 (+)-5,9α-Dimethyl-2-[3-(fluorobenzoyl)propyl]-2'hydroxy-6,7-benzomorpha·HC1



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

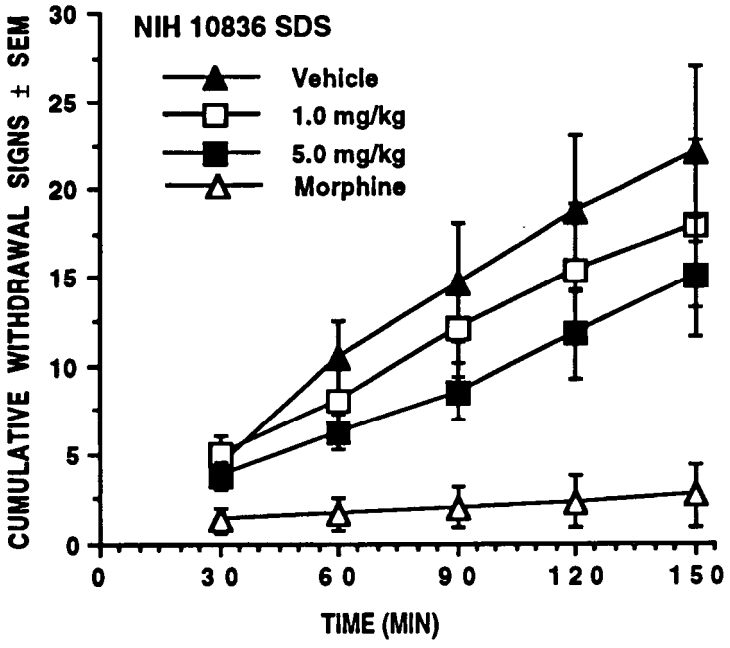
TF - 4.7 (2.5 - 9.1)[a,b]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a,b]
PPQ - 0.08 (0.03 - 0.23)
HP - 13% at 1.0, 10.0 and 30.0[a,b]

[a]Eyelid ptosis and reduced spontaneous activity, splayed limbs
[b]Vehicle - 5% hydroxypropyl-ß-cyclodextrin

MONKEY DATA
(SDS)

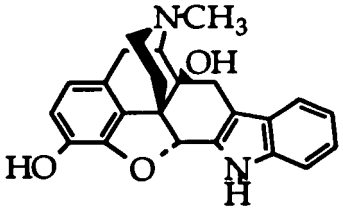
NIH 10836 neither substituted for morphine nor exacerbated withdrawal at doses of 1.0 and 5.0 mg/kg. The reduction in withdrawal scores, especially at the high dose was associated with slowing, eyelid ptosis, jaw sag, body jerks and "cataleptic" behavior. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in water.

NIH 10836 (Continued)



Comment: The biological profile suggests that NIH 10836 has little, if any, opioid effects and remarkable neuroleptic properties.

NIH 10842 Oxymorphindole·HCl



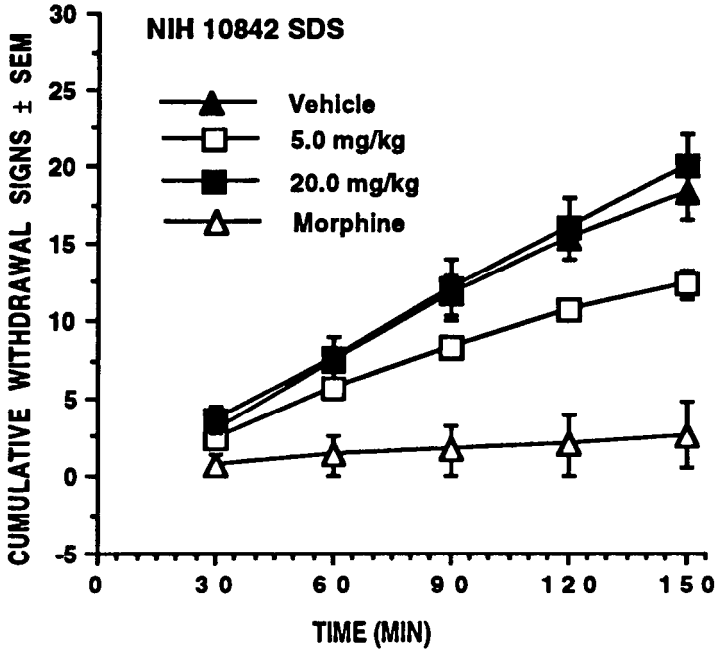
MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0 and 30.0
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - 9% at 1.0, 17% at 10.0 and 31% at 30.0
HP - Inactive at 1.0 and 30.0

MONKEY DATA
(SDS)

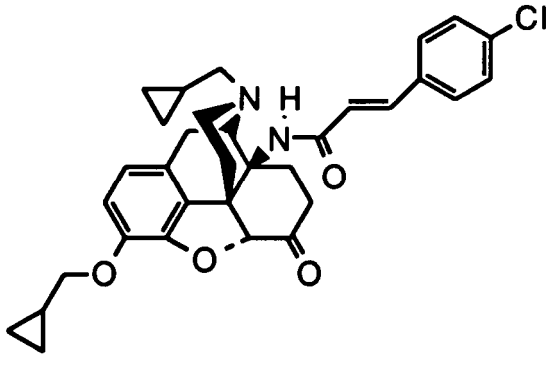
At 5 and 20 mg/kg, NIH 10842 neither substituted for morphine nor exacerbated withdrawal. Some reduction in withdrawal scores was observed at the low dose, however, this is not considered to be remarkable.

NIH 10842 (Continued)



Comment: This compound appears to be devoid of mu-opioid effects.

NIH 10844 14 ß-(*p*-Chlorocinnamoylamino)-3-cyclopropylmethoxy-N-cyclopropylmethyl-7,8-dihydromorphinone•oxalate (3-Cyclopropylmethyl-C-CAM) oxalate



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0 and 30.0[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 6.7 (2.2 - 20.7)[a]
HP - 13% at 1, 0, 25% at 10.0 and 0% at 30.0[a]

[a]Vehicle - 5% DMSO in water

Special Time-Course Study;

The results in the monkey SDS assay, which suggested long lasting antagonist activity, prompted us to conduct a time-course study for antagonism of morphine's antinociception in the tail-flick test in mice. The results (see table) indicate a very long duration of action for NIH 10844.

NIH 10844 (Continued)

Table. NIH 10844 time course vs morphine sulfate in mouse tail-flick test.

Time	AD50 or % antagonism
2 h	57% at 30 mg/kg
6 h	0.97 (0.39 - 2.42)
24 h	3.41 (1.37 - 8.50)
36 h	6.82 (3.13 - 12.76)
72 h	11.39 (4.14 - 31.36)

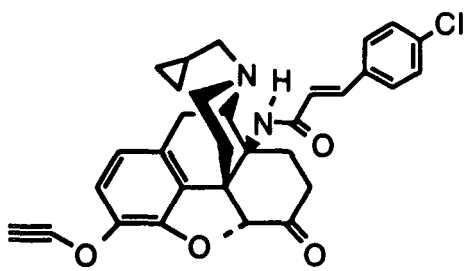
MONKEY DATA
(SDS)

An assay was initiated with a group of 4 monkeys 1 of which received 3 mg/kg of NIH 10844, another 0.75 mg/kg of NIH 10844, another 3 mg/kg morphine and another vehicle (10% DMSO in 10% hydroxypropyl-ß-cyclodextrin).

The two monkeys receiving NIH 10844 still vocalized after an injection of morphine at the termination of the experiment. The monkey receiving the high dose also had tremors. These two monkeys were found lying on their sides the next morning. Monkey 1301 (high dose) died at 9 A.M. that morning. A review of the medical records of this monkey revealed that it had a previous history of blood in the urine. In addition, at necropsy, blood was found in the capsules of both kidneys. Thus, it is very unlikely that an acute dose of NIH 10844 was responsible for the monkey's demise. Results of histology studies are pending.

Comment: NIH 10844 appears to be a potent and very long-acting opioid antagonist. If pathology reveals a chronic kidney condition, additional studies in morphine-dependent monkeys will be conducted.

NIH 10845 14ß-(*p* -Chlorocinnamoylamino)-N-cyclopropylmethyl-3-propargyl-7,8-dihydromorphinone
(3-Propargyl-C-CAM-oxalate)



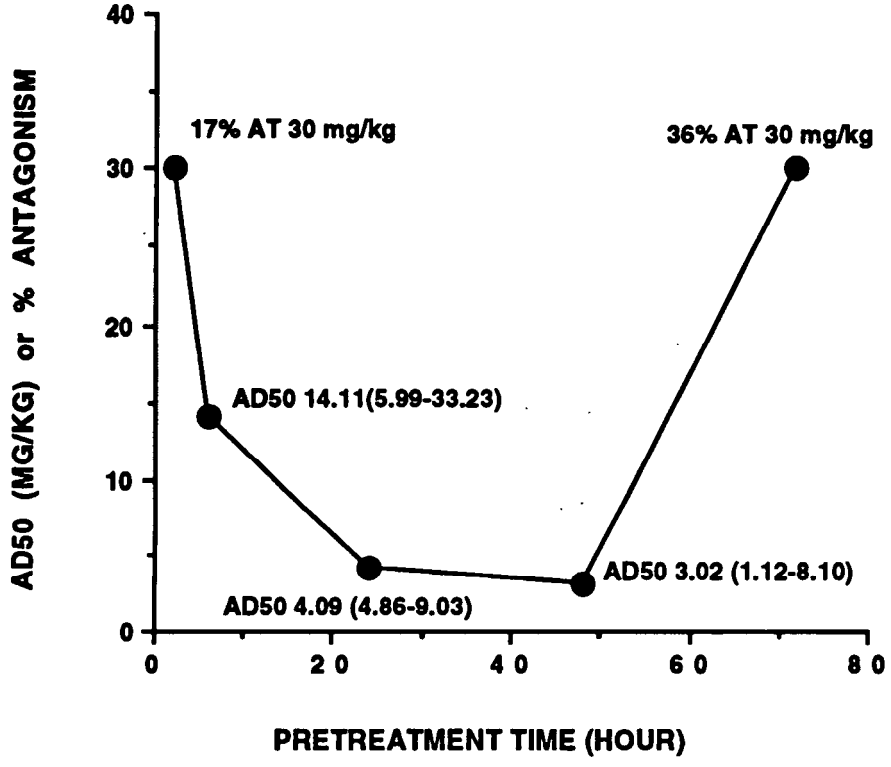
MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - 1.21 (0.57 - 2.88)[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 0.26 (0.09 - 0.82)[a]
HP - 0.26 (0.08 - 0.79)[a]

[a]Vehicle - 5% Hydroxypropyl-ß-cyclodextrin in water

Special - Mouse Time-Course Study. As shown in the accompanying graph, NIH 10845 manifested antagonist properties peaking between 24 and 48 h and lasting up to 72 h after its administration.

NIH 10845 (AD50) TIME COURSE vs MORPHINE SULFATE (ED80) IN T.F

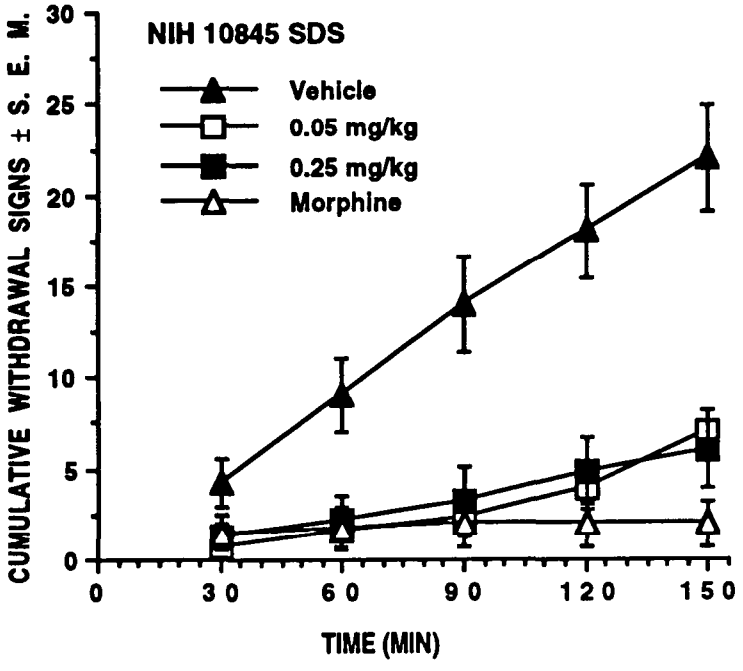


MONKEY DATA
(SDS)

Preliminary SDS. One monkey received a cumulative dose of 2.1 mg/kg over a 45-m interval. NIH 10845 substituted for morphine. However, during the next two days this primate showed withdrawal signs. On the second day after receiving the drug the monkey appeared much improved after receiving a double dose of morphine sulfate.

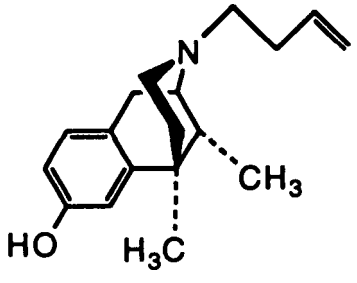
SDS. NIH 10845 dose-dependently substituted for morphine (see fig). Onset was rapid. However, duration was waning after 90 m. At peak effect, potency was estimated to be 60 x that of morphine sulfate. One monkey receiving 1.0 mg/kg (data not shown, n = 1) was also found in withdrawal on the following day. A double dose of morphine seemed to attenuate withdrawal. Also, shortly after receiving NIH 10845, the animal appeared to be stimulated. In addition, buccal movements were observed. Two other monkeys bled from the penis. One of these received NIH 10845 and the other morphine. They recovered after antibiotic therapy. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in water.

NIH 10845 (Continued)



Comment: NIH 10845 behaved as mu agonist and later, perhaps after it was metabolized, as an irreversible antagonist. This is not readily apparent in the monkey study because the doses were kept low to avoid prolonged withdrawal. However, the results of the mouse, time-course study support this premise.

NIH 10847 (-)-2-(3-Butenyl)-5,9α-dimethyl-2'-hydroxy-6,7-benzomorphan·HCl



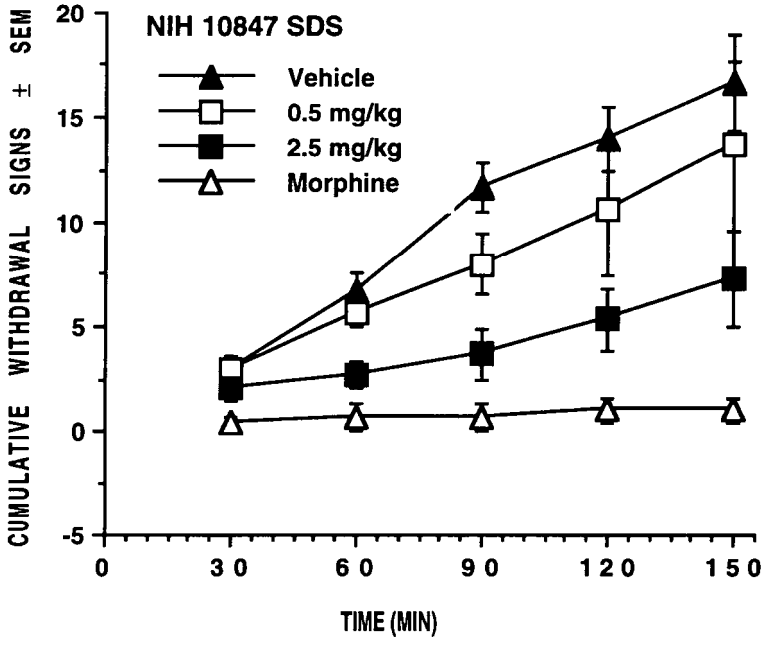
MOUSE DATA - ED50 OR AD50, mg/kg/s.c. (95% C.L.) or % change

TF- 0.5 (0.1 - 1.5)
TP vs M - 3.8 (1.2 - 12.3)
PPQ - 0.3 (0.1 - 0.7)
HP - 0.8 (0.3 - 2.2)

MONKEY DATA
(SDS)

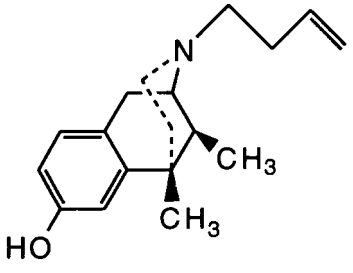
As shown in the accompanying figure, NIH 10847 produced a dose-related reduction or attenuation of withdrawal signs; however, this action was accompanied by the signs slowing, jaw sag, ataxia and eyelid ptosis. At the high dose, onset of action was prompt and duration was at least 2 1/2 h.

NIH 10847 (Continued)



Comment: The mouse data suggests agonist/antagonist or partial agonist activity. It is uncertain at this time whether the behavioral effects noted in monkeys are opioid-like.

NIH 10848 (+)-2-(3-Butenyl)-5,9α--dimethyl-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50, mg/kg/s.c. (95% C.L.) or % change

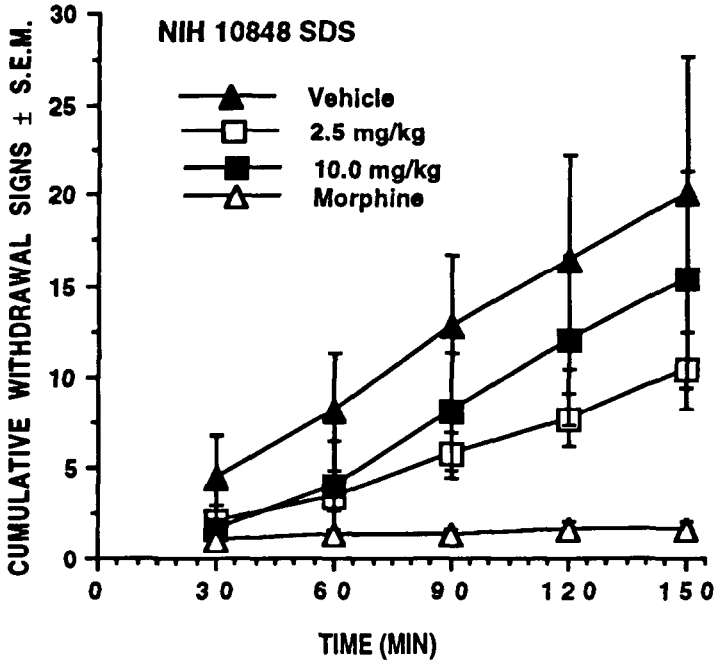
TF - Inactive at 1.0, 10.0 and 30.0
TF vs M - Inactive at 1.0, 10.0 and 30.0
PPQ - 17.0 (11.0 - 26.1)
HP - Inactive at 1.0 and 10.0 and 13% at 30.0[a]

[a]Increased locomotor activity, ataxia and Straub tail at 30.0 mg/kg

MONKEY DATA
(SDS)

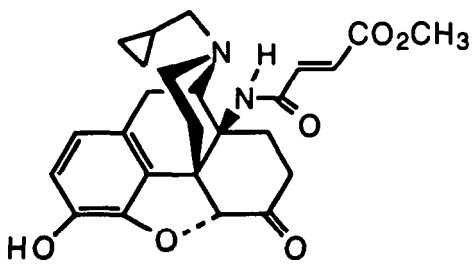
NIH 10848 neither substituted for morphine nor exacerbated withdrawal. At both doses, behavioral signs were observed. At the high dose, ataxia, sagging, slowing, "confusion," and difficulty in walking and getting off perch. The apparent reduction in withdrawal scores (see fig.) may reflect extraopioid CNS effects.

NIH 10848 (Continued)



Comment: The profile of activity does not suggest mu-opioid properties.

NIH 10849 N-Cyclopropylmethyl-7,8-dihydro-14ß-[3'-methoxycarbonyl)propenamido]-normorphinone·oxalate



MOUSE DATA - ED50 OR AD50, mg/kg/s.c. (95% C.L.) or % change

TF - 1.2 (0.5 - 2.6)
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - 1.5 (0.6 - 3.5)
HP - 1.8 (0.6 - 5.1)[a]

[a]At 5 and 10 mg/kg, increased locomotion and Straub tail were observed.

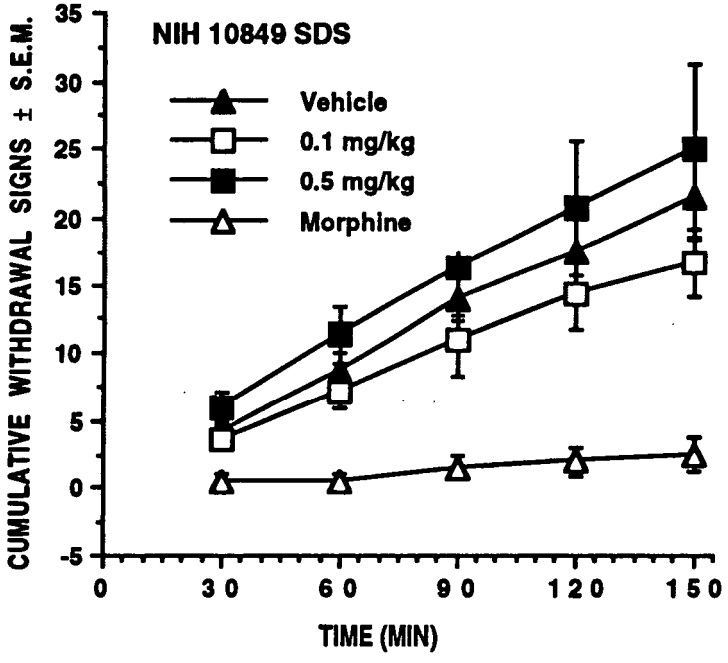
MONKEY
(SDS)

At does of 0.1 and 0.5 mg/kg, NIH 10849 did not substitute for morphine or attenuate abrupt withdrawal (see fig.). At the high dose, there was some indication that this compound exacerbated withdrawal as indicated by the increased frequency of wet-dogs and aggressive behavior. Cat-like stretching was also observed.

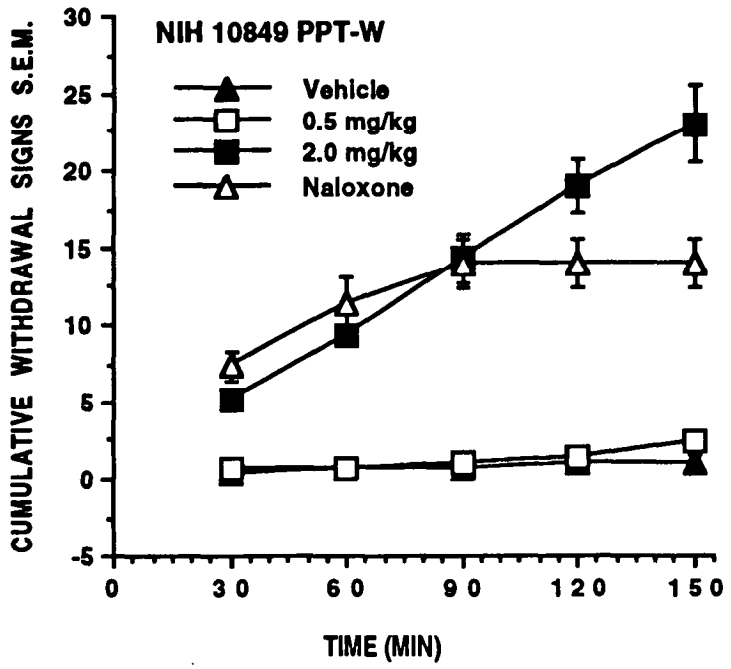
NIH 10849 (Continued)

(PPt-W)

As shown in the accompanying figure, NIH 10849 precipitated withdrawal at the high dose. Onset was prompt and duration of action was at least 2 1/2 h. In this experiment, the naloxone controls exhibited a less intense withdrawal syndrome than is commonly observed so that a potency estimate. is difficult. A crude estimate would be that NIH 10849 is 100 x less potent than naloxone. However, its duration of action is definitely longer than that of naloxone.

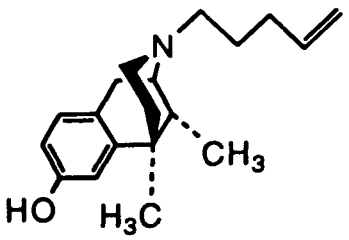


NIH 10849 (Continued)



Comment: Mouse data suggests that NIH 10849 has mu agonist properties. In the monkey, this compound evokes a mu-opioid-like withdrawal syndrome. Aside from metabolic considerations, the drug may have partial agonist properties.

NIH 10852 (-)-5,9α-Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-bennzomorphan·HCl



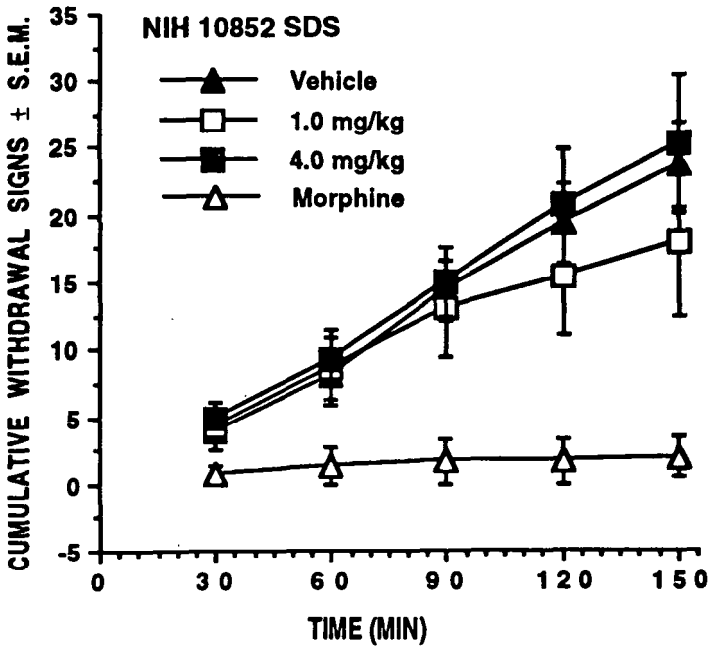
MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - Inactive at 3.0, 10.0 and 30.0, 20% at 1.0[a,b]
TF vs. M - 6.1 (2.2 - 16.9)
PPQ - 1.4 (0.6 - 3.5)
HP - 0% at 1.0, 13% at 10.0 and 38% at 30.0

[a]Vehicle 5% hydroxypropyl-ß-cyclodextrin
[b]At 10.0 and 30.0 slight ataxia, increased locomotor activity and moderate Straub tail observed.

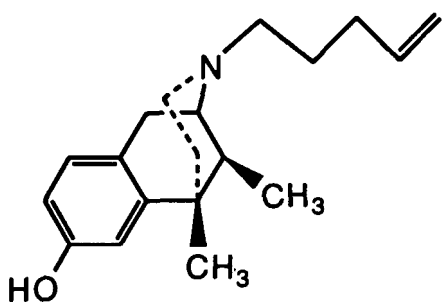
MONKEY DATA
(SDS)

Up to doses that produced slowing and ataxia, NIH 10852 neither substituted for morphine nor exacerbated withdrawal. The results are depicted in the accompanying figure. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in sterile water.



Comment: The data suggests very weak opioid agonist and antagonist activity. However, studies in the morphine-dependent monkey were not remarkable. Metabolic differences may underlie variation between the mouse and monkey.

NIH 10853 (+)-5,9α-Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

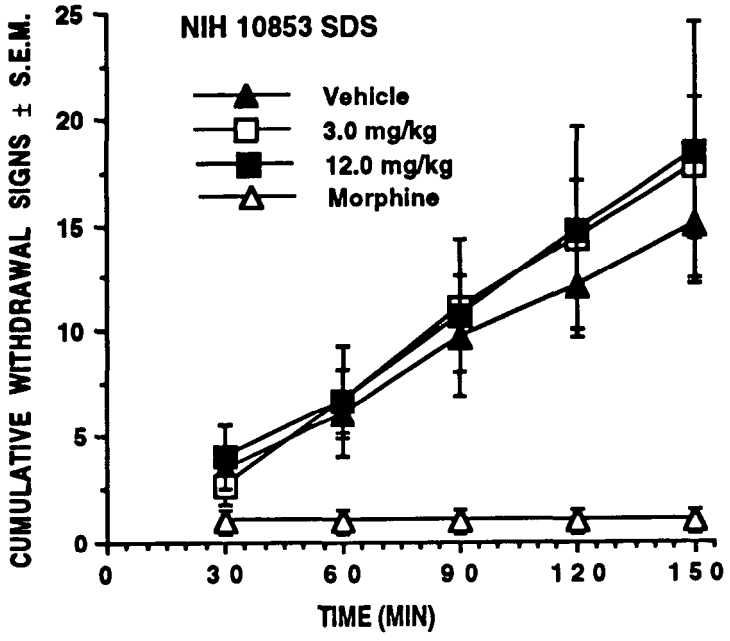
TF - Inactive at 1.0, 10.0 and 30.0[a]
TF vs. M - 21% at 1.0, Inactive at 10.0 and 30.0
PPQ - Inactive at 1.0, 10.0 and 30.0
HP - Inactive at 1.0, 10.0 and 30.0

[a]Vehicle - 5% Hydroxypropyl-ß-cyclodextrin in aqueous solution.

MONKEY DATA
(SDS)

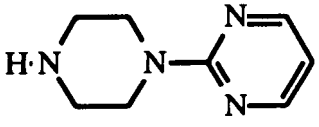
As shown in the fig., NIH 10853 neither substituted for morphine nor exacerbated withdrawal. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in sterile water.

NIH 10853 (Continued)



Comment: Apparently, NIH 10853 is devoid of opioid activity.

NIH 10854 1-(2-Pyrimidinyl)piperazine·2HCl (I-PP)



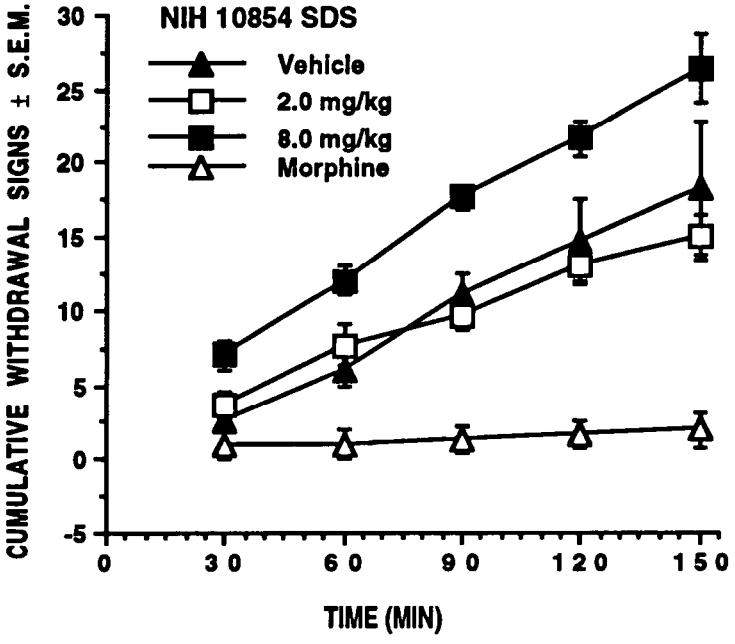
MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0 and 30.0
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - Inactive at 1.0, 10.0 and 30.0
HP - 13% at 1.0 and 10.0, inactive at 30.0

MONKEY DATA
(SDS)

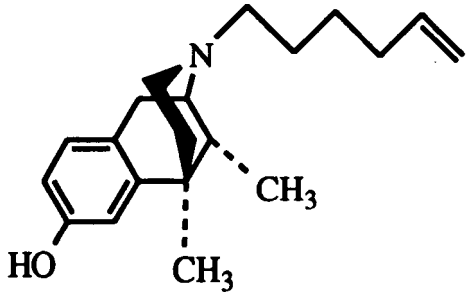
I-PP is a major metabolite of buspirone which we reported to attenuate opiate withdrawal and cocaine hyperarousal., This compound is reported to inhibit dorsal raphe firing at 3.0 mg/kg and to be active in the Vogel anticonflict paradigm. It also displaced clonidine. As shown in the figure, it did not substitute for morphine and at the high dose may have possibly exacerbated withdrawal. The latter effect may be an artifact due to the low order of withdrawal noted in the vehicle controls.

NIH 10854 (Continued)



Comment: Apparently I-PP does not interact with the opiatergic system.

NIH 10855 (-)-5,9α-Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - 0.8 (0.4 - 1.5)[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 0.3 (0.1 - 0.6)[a]
HP - 0.6 (0.1 - 2.2)[a,b]

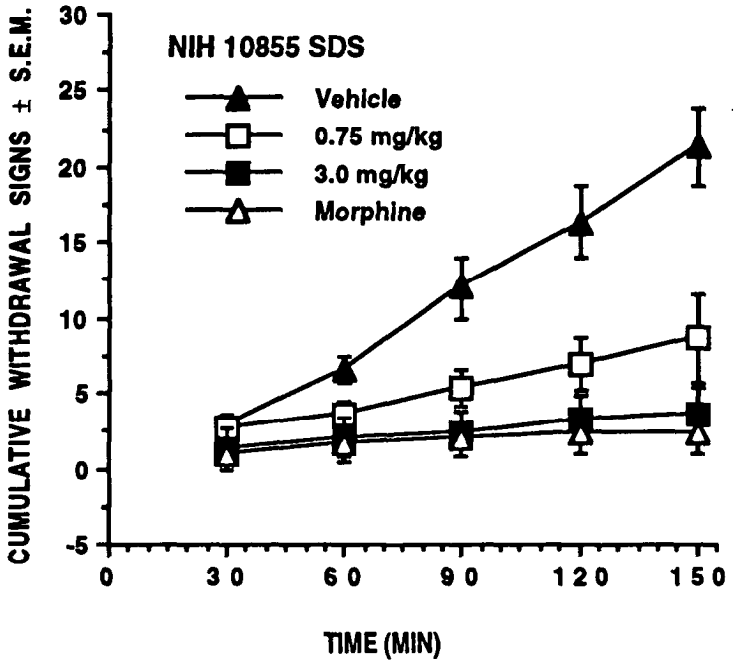
[a]Vehicle 5% hydroxypropyl-ß-cyclodextrin
[b]Straub tail, increased locomotor activity at 30.0

Special Test: Naloxone AD_{50} vs ED_{80} of NIH 10855 in TF = 0.04 (0.01 - 0.11)

MONKEY DATA
(SDS)

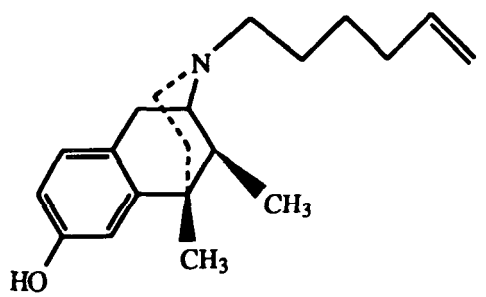
NIH 10855 substituted completely for morphine at 3.0 mg/kg (see fig.) without producing overt behavioral effects. Onset and duration of action were similar to those of morphine as was the potency estimate. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in sterile water.

NIH 10855 (Continued)



Comment: The profile of activity is reminescent of that of morphine.

NIH 10856 (+)-5,9α-Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-bennzomorphan·HCl



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - Inactive at 1.0 and 30.0, 14% at 10.0[a]
TP vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 6% at 1.0 and 10.0, 31% at 30.0[a]
HP - 0% at 1.0 and 10.0, 25% at 30.0[a]

[a]Vehicle was 5% hydroxypropyl-ß-cyclodextrin

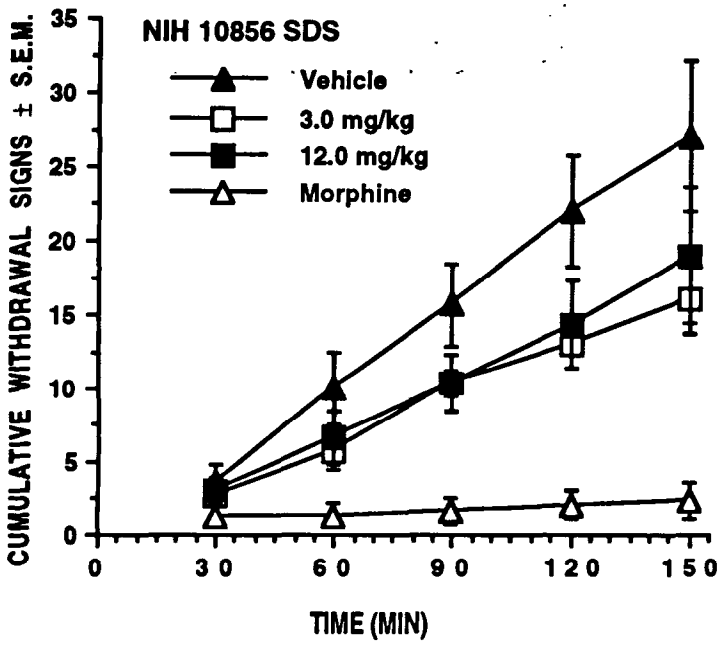
MONKEY DATA
(SDS)

Preliminary SDS
After receiving a cumulative dose of 15.0 mg/kg (1, 2, 4, and 8 mg/kg at 15 m intervals), the monkey had convulsions that were terminated using 30 mg of pentobarbital i.p.

NIH 10856 (Continued)

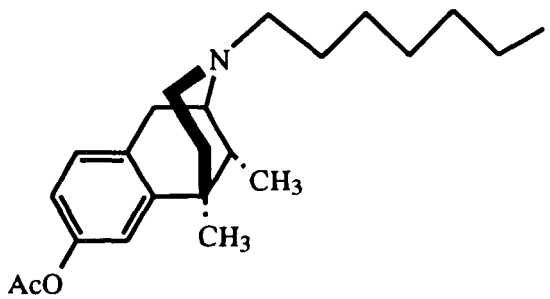
SDS

As shown in the figure, NIH 10856 produced a non dose-related reduction in withdrawal signs at 3.0 and 12.0 mg/kg. The effect was not significant when the results are compared with those of vehicle controls. Some slowing was noted at the high dose. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in sterile water.



Comment: It does not appear likely that NIH 10856 has significant opioid activity.

NIH 10857 (-)-2'-Acetoxy-5,9 α-dimethyl-2-heptyl-6,7-bennzomorphan•HCl



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - 5.6 (3.0 - 10.3)[a,d]; 3.8 (2.6 - 5.6)[b,c,d]
TF vs. M - 0% at 1.0, 10.0 and 30.0[a,b,c,d]
PPQ - 1.3 (0.7 - 2.5)[a,d]; 0.7 (0.3 - 2.0)[b,d]
HP - 3.0 (1.2 - 8.0)[a,c,d]; 1.9 (1.0 - 3.7)[b,c,d]

[a]Regular 20 m pretreatment.
[b]One h pretreatment.
[c]Straub tail at 10.0 and 30.0, increased locomotor activity at 30.0.
[d]Vehicle was 5% hydroxypropyl-ß-cyclodextrin.

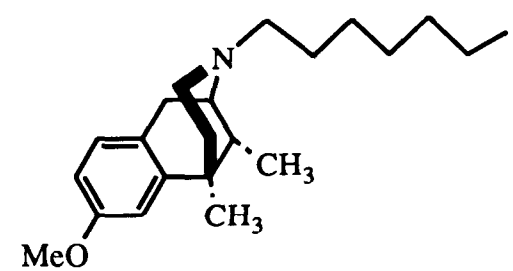
MONKEY STUDY
(SDS)

Preliminary SDS

Ten m after receiving a cumulative dose of 15 mg/kg (1, 2, 4 and 8 mg/kg), the monkey had convulsions which were terminated with 30 mg of pentobarbital i.p. The monkey expired without regaining consciousness. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in sterile water.

Comment: Unless there is unusual interest in this compound, further studies in the monkey are not recommended at this time.

NIH 10858 (-)-5,9α-Dimethyl-2-heptyl-2'-methoxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0, 40% at 30.0[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - 9.4 (3.6 - 24.5)
HP - Inactive at 1.0, 10.0 and 30.0[b]

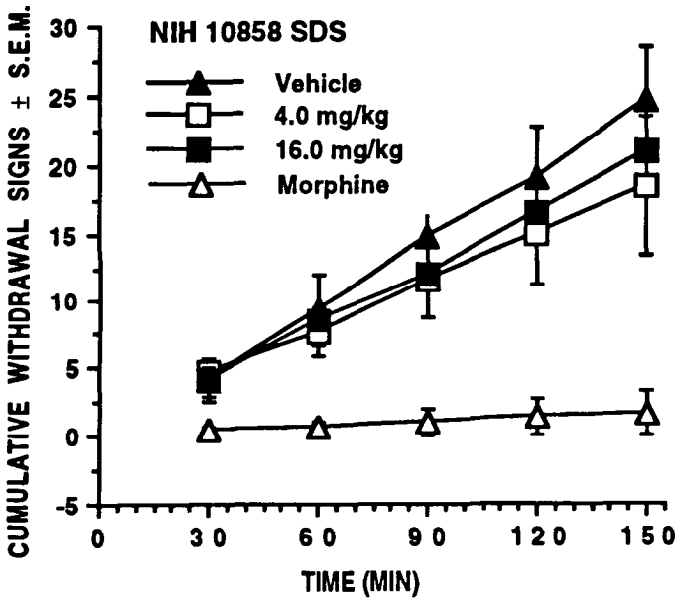
Vehicle: 5% Hydroxypropyl-ß-cyclodextrin in water

[a]Increased locomotor activity
[b]Some ptosis, decreased locomotor activity

NIH 10858 (Continued)

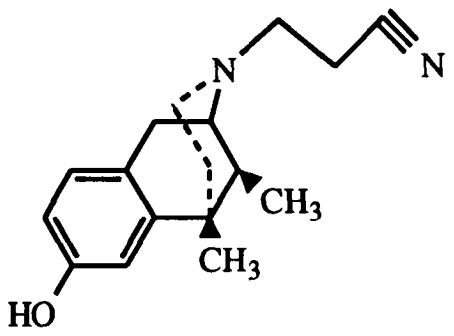
MONKEY DATA
(SDS)

As shown in the graph, NIH 10858 did not substitute for morphine or exacerbate withdrawal. One monkey receiving the high dose became ataxic and fell off the perch. This animal was given morphine however, later it convulsed. Two doses of 30 mg of pentobarbital were given to control convulsions and then the monkey was placed in a small holding cage. It recovered eventually.



Comment: NIH 10858 does not appear to possess mu-opioid activity.

NIH 10862 (+)-2-(2-Cyanoethyl)-5,9α-dimethyl-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0 and 30.0[a]

TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]

PPQ - Inactive at 1.0, 14% at 10.0 and 26% at 30.0[a]

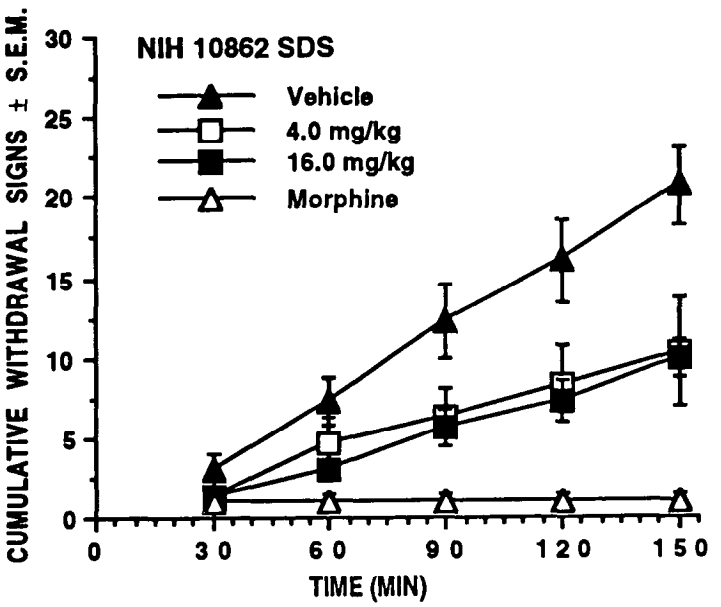
HP - 13% at 1.0, 25% at 10. and 20% 30.0[a]

[a]Vehicle - 2.5% hydroxypropyl-ß-cyclodextrin in water

NIH 10862 (Continued)

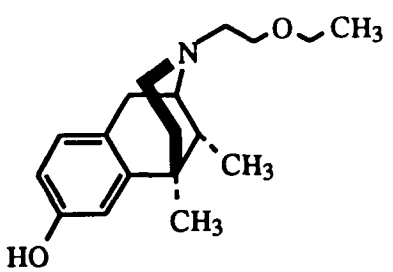
MONKEY DATA
(SDS)

NIH 10862 neither substituted for morphine nor exacerbated withdrawal at doses of 3 and 12 mg/kg (see fig.). Vehicle was 10% hydroxypropyl-ß-cyclodextrin in water.



Comment: Apparently, NIH 10862 is without significant effect regarding antinociception in the mouse and opioid activity in the monkey.

NIH 10863 (-)-5,9α-Dimethyl-2-(2-ethoxyethyl)-2'-hydroxy-6,7-benzomorphan·oxalate



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - 1.08 (0.54 - 2.15)[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 0.35 (0.13 - 0.96)[a]
HP - 0.85 (0.32 - 2.25)[a]

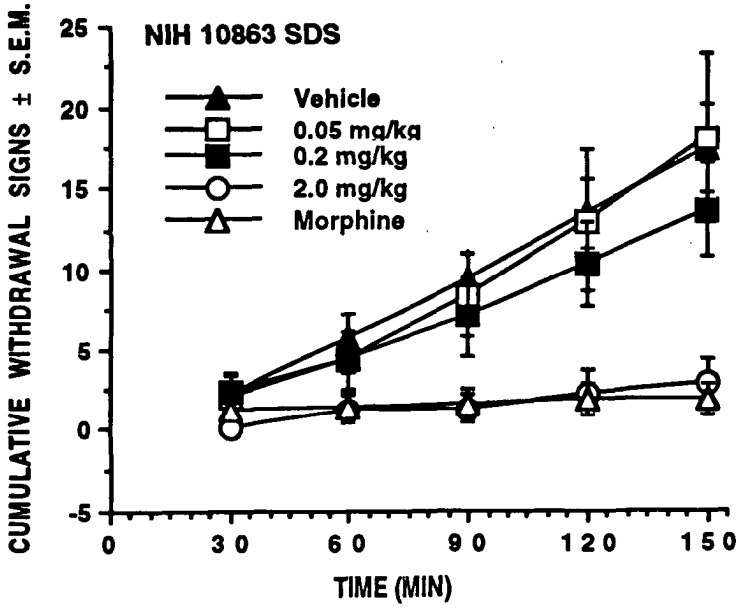
[a]Vehicle - 2.5% hydroxypropyl-ß-cyclodextrin in water

Special: Naloxone vs NIH 10863 in TF, AD_{50} = 0.04 (0.03 - 0.26)[a]

NIH 10863 (Continued)

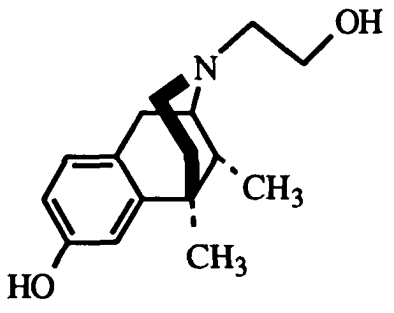
MONKEY DATA
(SDS)

At a dose of 2.0 mg/kg, NIH 10863 substituted completely for morphine (see fig). However, at this dose signs designated jaw sag, eyelid ptosis, salivation and slowing were noted. Potency appears to be equivalent to morphine. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in water.



Comment: NIH 10863 behaved essentially as a mu opioid agonist in the mouse TF test and in the monkey SDS assay.

NIH 10864 (-)-5,9-α-Dimethyl-2'-hydroxy-2-(2-hydroxyethyl)-6,7-benzomorphan•oxalate



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0 and 30.0[a]

TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]

PPQ - Inactive at 1.0, 14% at 10.0 and 26% at **30.0**[a]

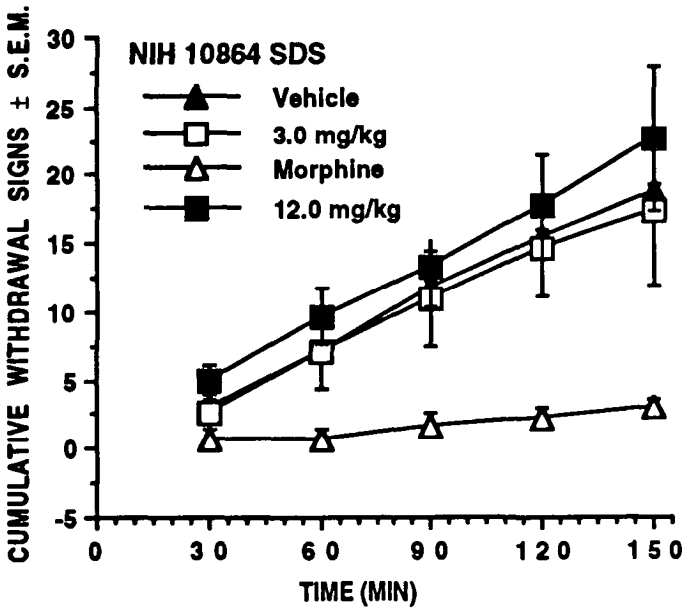
HP - 13% at 1.0, 25% at 10. and 20% 30.0[a]

[a]Vehicle - 2.5% hydroxypropyl-ß-cyclodextrin in water

NIH 10864 (Continued)

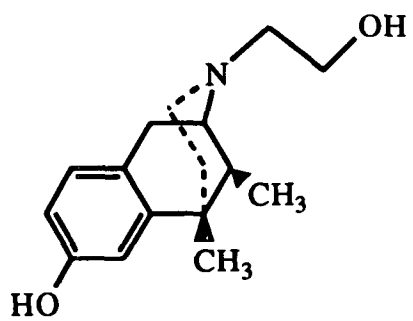
MONKEY DATA
(SDS)

NIH 10864 neither substituted for morphine nor exacerbated withdrawal at doses of 3 and 12 mg/kg. Vehicle was 10% hydroxypropyl-ß-cyclodextrin in water.



Comment: Apparently, NIH 10864 was without significant opioid effect in the mouse and monkey studies.

NIH 10865 (+)-5,9-α-Dimethyl-2'-hydroxy-2-(2-hydroxyethyl)-6,7-benzomorphan•oxalate



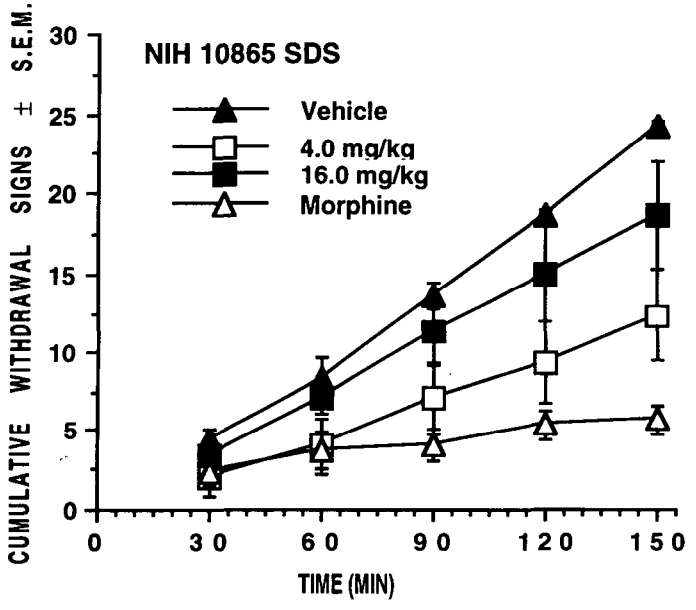
MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - Inactive at 1.0, 10.0 and 30.0
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - Inactive at 1.0, 10.0 and 30.0
HP - 25% at 1.0, 0% at 10.0 and 30.0

NIH 10865 (Continued)

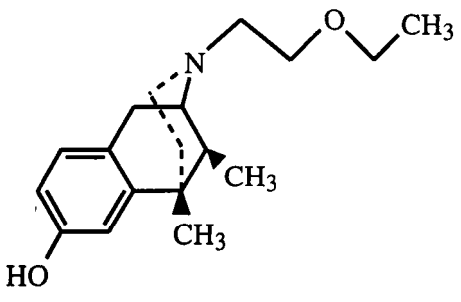
MONKEY DATA
(SDS)

The inverse dose response attenuation of withdrawal scores shown in the fig is probably an artifact. At both doses, attenuation was associated principally with a reduction in the sign designated rigid abdominal muscles and vocalization when abdomen was palpated. Reduction in the number of these behavioral scores suggests antinociceptive activity.



Comment: This compound has an unusual profile, namely, lack of activity in the mouse and potential analgesic properties in the monkey. Additional pharmacokinetic studies may be indicated in the mouse.

NIH 10866 (+)-5,9α-Dimethyl-2-(2-ethoxyethyl)2'-hydroxy-6,7-benzomorphan•oxalate



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

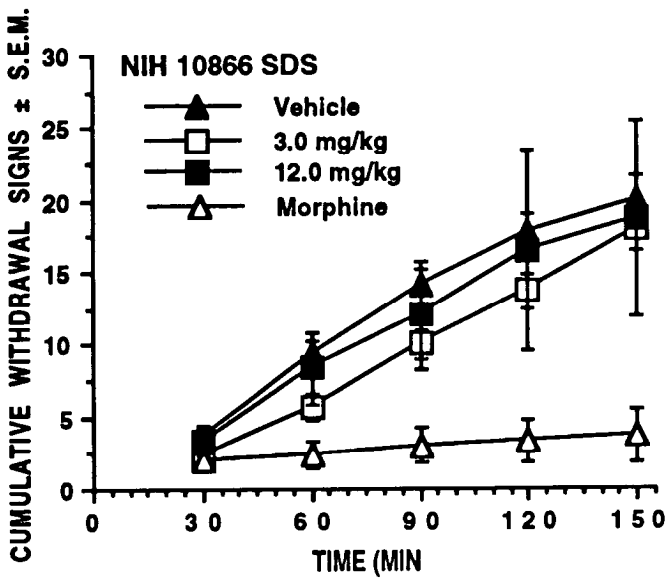
TF - Inactive at 1.0, 10.0 and 30.0[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.0[a]
PPQ - 6% at 1.0, 14% at 10.0 and 29% at 30.0[a]
HP - Inactive at 1.0, 10.0 and 30.0[a]

[a]Vehicle - 2.5% hydroxypropyl-ß-cyclodextrin in water.

NIH 10866 (Continued)

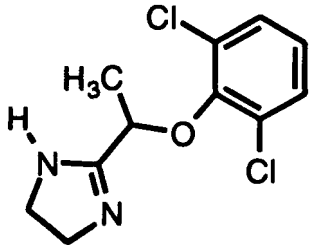
MONKEY DATA
(SDS)

No remarkable effects were noted with NIH 10866 in the SDS assay (see accompanying fig.). Vehicle was 10% hydroxypropyl-ß-cyclodextrin in water.



Comment: NIH 10866 seems devoid of opioid activity in the mouse antinociceptive tests and in withdrawn morphine-dependent monkeys.

NIH 10868 (2-[1-(2,6-Dichlorophenoxy)ethyl]4,5dihydro-1H-imidazole (Lofexidine)



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - 0.4 (0.2 - 1.1)[a]
TF vs. M - Inactive at 1.0, 10.0 and 30.00
PPQ - 0.01(0.006 - 0.03)
HP - 25% at 1.0 and 1.0, 63% at 30.0[b]

[a]At 1.0, ataxia, piloerection, blanched ears and immobility were noted; at 0.1 and 0.3, piloerection and ataxia were seen.

[b]At 1.0, abnormal gait and piloerection were observed. At 10.0, increased locomotion, vocalization, hopping and stiff tails, and at 30.0 mg/kg hopping movements, increased locomotion followed by immobility and Straub tails were recorded.

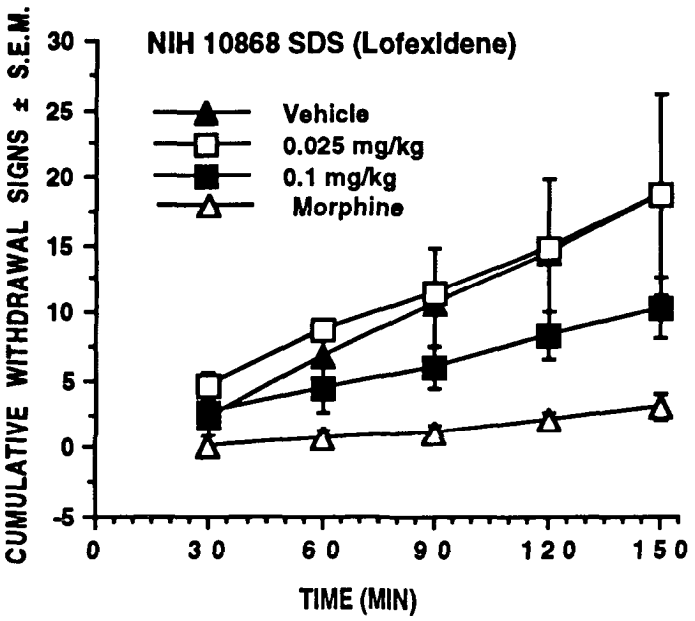
Special Test: Naloxone AD50 vs ED80 of NIH 10868 in TF

Naloxone (mg/kg)	% Antagonism of ED80 of NIH 10868
0.3	18
1.0	47
1.0	28
3.0	40
10.0	58

MONKEY DATA
(SDS)

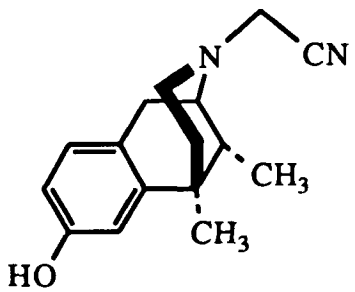
NIH 10868 attenuated withdrawal in a dose-related manner at doses of 0.025 and 0.1 mg/kg. The highest, namely 0.4 mg/kg, was no more effective than the 0.1 mg/kg dose indicating a limited dose-response action (see fig.) In addition, at the highest dose, the signs designated slowing, drowsiness, jaw and body sag and eyelid ptosis were noted.

NIH 10868 (Continued)



Comment: In the mouse, NIH 10868 displayed antinociceptive activity which was only partially antagonized by high doses of naloxone. In the monkey, attenuation of withdrawal was observed. However, the effect was self-limited and attended by a variety of side effects at the highest dose.

NIH 10869 (-)-2-Cyanomethyl-5,9 α-dimethyl-2'-hydroxy-6,7-benzomorphan·HCl



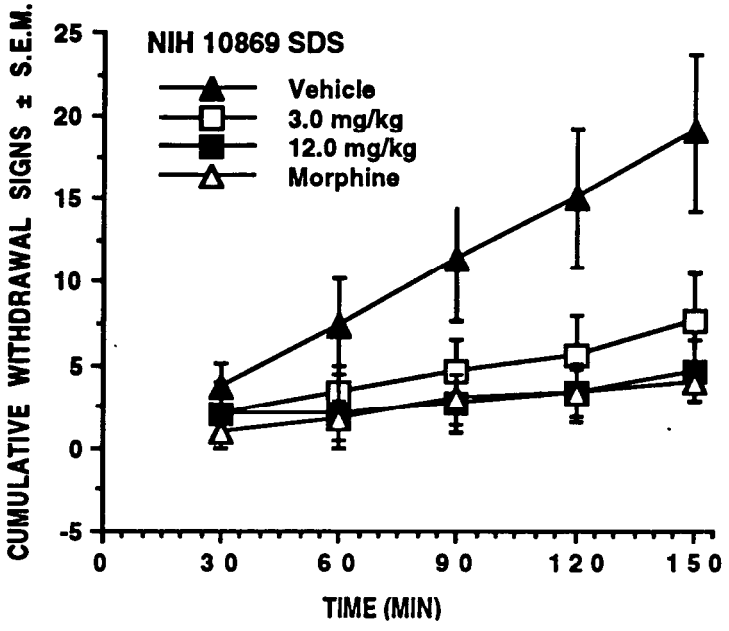
MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - 11.60 (4.80 - 28.10)
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - 1.52 (0.50 - 4.7)
HP - 8.50 (3.20 - 22.5)

MONKEY DATA
(SDS)

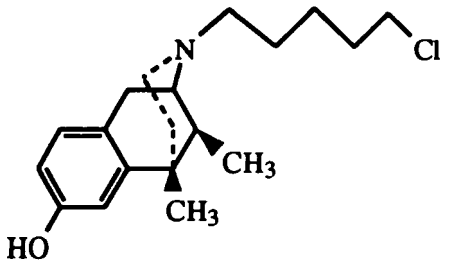
NIH 10869 substituted completely for morphine at 12 mg/kg (see fig.) However, at this dose the signs jaw sag, slowing, ataxia, eyelid ptosis and salivation were noted. Nevertheless, the lower dose nearly substituted for morphine with no accompanying side effects. Potency is estimated to be 1/4 that of morphine.

NIH 10869 (Continued)



Comment: NIH 10869 displays a mu opioid profile of activity in the mouse and monkey.

NIH 10872 (+)-2-(5-Chloropentyl)-5,9α-dimethyl-2'-hydroxy-6,7-benzomorphan·HCl



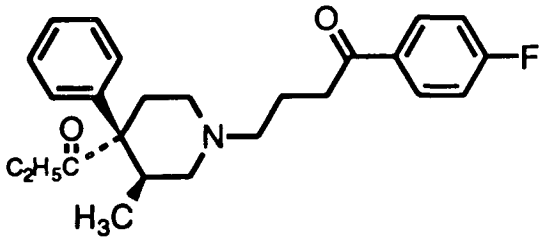
MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

TF - 0% at 1.0, 21% at 10.0 and 10% at 30.0
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - 4.6 (2.4 - 8.7)
HP - 0% 1.0, and 10.0 and 25% at 30.0

MONKEY DATA
(SDS)

Comment: The results in the mouse do not portend opioid activity.

NIH 10873 (+)-N-3(p-Fluorobenzoyl)propyl-3ß-methyl-4-phenyl-4-propionyloxypiperidine•HCl

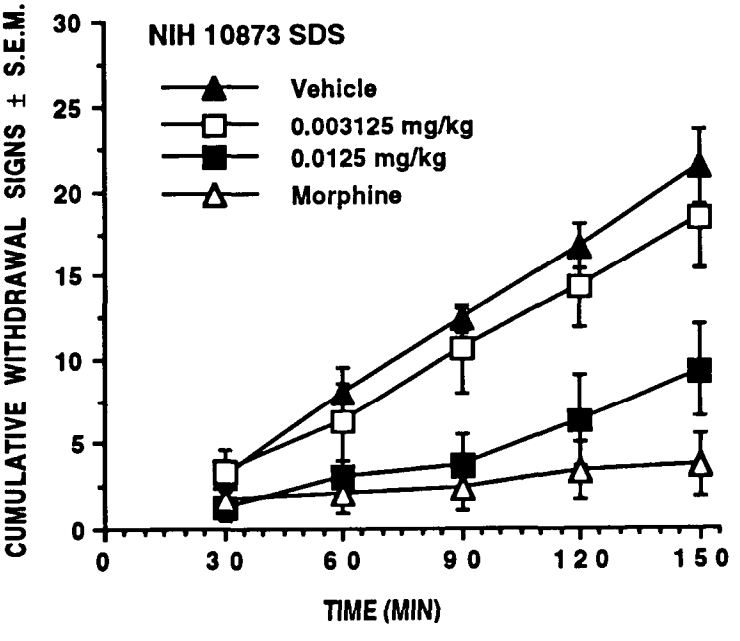


MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change

TF - 0.5 (0.2 - 1.0)
TF vs. M - Inactive at 1.0, 10.0 and 30.0
PPQ - 0.09 (0.04 - 0.18)
HP - 0.5 (0.2 - 1.0)

MONKEY DATA
(SDS)

The accompanying figure depicts a dose-dependent attenuation of withdrawal signs. Onset of action was slightly delayed and offset was somewhat shorter than that of morphine sulfate, the positive control. In the dose range tested, NIH 10873 did not completely alleviate withdrawal. Perhaps higher doses might have substituted completely.



Comment: NIH 10873 has a profile indicating mu-opioid agonist activity.

NIH 10891 Enkephalin, [D-Ala^2-,N-Me-Phe^4,Gly-ol^5] (DAMGO)

H_2N-Tyr-D- Ala-Gly-N-Me-Phe-Gly-ol

SPECIAL MOUSE DATA[a]

[a]See TABLES 4, 6, 7, 8 and 9.

NIH 10892 Enkephalin, [D-Pen^{2,5}] (DPDPE)

H-Tyr-D-Pen-Gly-Phe-D-Pen-OH

SPECIAL MOUSE DATA[a]

[a]See TABLES 4 and 9.

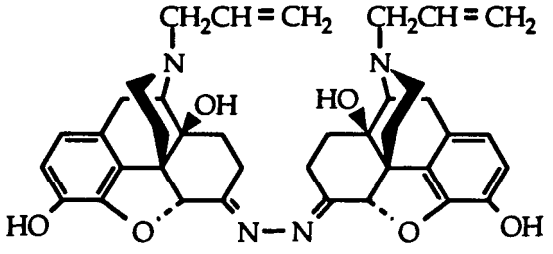
NIH 10893 ICI 174,864 N,N-Diallyl-Tyr-Aib-Aib-Phe-Leu-OH
(Aib=α-aminoisobutyric acid)

N,N-Diallyl-Tyr-Aib-Aib-Phe-Leu-OH

SPECIAL MOUSE DATA[a]

[a]See TABLE 8

NIH 10894 *bis*[5α-4,5-Epoxy-3-14-dihydroxy-17-(2-propenyl)-morphinan-6-ylidene]hydrazine (Naloxonazine)



SPECIAL MOUSE DATA[a]

[a]See Table 7

ACKNOWLEDGMENTS

This study was was supported by contracts DA 3-8200 and DA 5-8059 from the National Institute on Drug Abuse. We also acknowledge the expert assistance of Susan M. Scates, Larry Hughes and Zhen Ji. We thank Laura Johnson for her assistance in the preparation of this manuscript.

REFERENCES

Aceto, M.D., Flora, R.E. and Harris, L.S. The effects of naloxone and nalorphine during the development of morphine dependence in rhesus monkeys. Pharmacol, 15: 1-9 1977.

Aceto, M.D., Flora, R.E. and Harris, L.S. Caffeine elicited withdrawal signs in morphine-dependent rhesus monkeys. Eur J Pharmacol, 50:203-207, 1978.

Aceto, M.D., McKean, D.B. and Pearl, J. Effects of opiates and opiate antagonists on the Straub tail reaction in mice. Br J Pharmacol, 36:225-239, 1969.

Atwell, L. and Jacobson, A.E. The search for less harmful analgesics. I.ab Animal, 7:42-47, 1978.

D'Amour, F.E. and Smith, D.L. A method for determninating loss of pain sensation. J Pharmacol Exp Ther, 72:74-79, 1941.

Crain, S.M. and Schen, K.-F. Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine in sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment. Proc. Natl. Acad, Sci. 92: 1-5, 1995.

Deneau, G.A. An analysis of factors influencing the development of physical dependence to narcotic analgesics in the rhesus monkey with methods for predicting physical dependence liability in man. Doctoral Dissertation, University of Michigan, 1956.

Dewey, W.L., Harris, L.S., Howes, J.F. and Nuite, J.A. The effects of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tests. J Pharmacol Exp Ther, 175:435-552, 1970.

Dewey, W.L. and Harris, L.S. Antinociceptive activity of the narcotic antagonists analogues and antagonistic activity of narcotic analgesics in rodents. J Pharmacol Exp Ther 179:652-659, 1971.

Eddy, N. B. and Leimbach, D. Synthetic analgesics. II. Dithienylbutenyl- and dithienylbutylamines. J Pharmacol Exp Ther, 107:385-393, 1953.

Jacobson, A.E. and May, E.L. Structures related to morphine. XXXI. 2'-Substituted benzomorphans. J Med Chem. 8:563-566, 1965.

Pearl, J. and Harris, L.S. Inhibition of writhing by narcotic antagonists. J Pharmacol Exp Ther, 154, 319, 1966.

Schild, M.O. pA_2, A new scale for the measurement of drug antagonism. Br J Pharmacol, 2:189-206, 1947.

Seevers, M.H. Opiate addiction in the monkey. I. Methods of study. J Pharmacol Exp Ther, 56: 147-156, 1936.

Seevers, M.H. and Deneau, G.A. Physiological aspects of tolerance and physical dependence. In: Root, W.S. and Hofman, F.G., eds. Physiological Pharmacology, Vol. I. New York: Academic Press, 1963. pp. 565-570.

Tallarida, R.J. and Murray, R.B. Manual of pharmacological calculations with computer programs. Second Edition: New York: Springer-Verlag, 1987. pp. 53-56.

Teiger, D.G. Induction of physical dependence on morphine, codeine, and meperidine in the rat by continuous infusion. J Pharmacol Exp Ther, 190:408-415, 1974.

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EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (1996)

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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 arc 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 MC 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 15-min 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, l5-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 (40%) 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 arc 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, 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, 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,. The last 3 minutes of exposure to CO, 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 inter-injection 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.,* 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.

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 NaCI.

** 1R-5R-9R-2"R-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan hydrochloride

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 (DAMGG); (μ selective),
[D-Per^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 reversible κ receptor antagonist norbinaltorphimine (Smith et al., 1989) and the competitive δ 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 moddified Kreb's physiological buffer. The buffer contains the following (mM): NaCl, 118; KCl, 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	
ß-FNA	6.99	43.9	
ß-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	13100	
U69,593	38000	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 ß-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

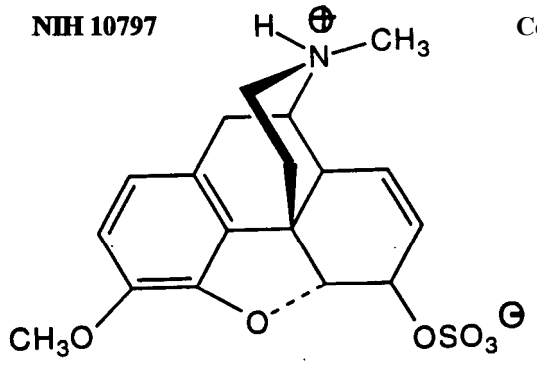
NIH #	SA	MVD	BIND	DD	ANLG	RSP	REPORT*
10797	-	+	+	-	-	-	3/22/93
10798	-	+	+	-	-	-	5/7/93
10806	-	+	+	-	-	-	2/2/94
10807	-	+	+	-	-	-	2/2/94
10808	-	+	+	-	-	-	2/2/94
10815	-	-	MCB	-	-	-	2/2/94
10826	-	-	MCB	-	-	-	5/2/94
10827	-	-	MCB	-	-	-	5/20/94
10831	-	-	MCB	-	-	-	5/20/94
10832	-	-	MCB	-	-	-	7/27/94
10834	-	+	MCB	-	-	-	2/15/95
10835	-	+	MCB	-	-	-	2/15/95
10836	-	+	MCB	-	-	-	2/15/95
10847	-	+	MCB	-	-	-	3/24/95
10848	-	+	MCB	-	-	-	3/24/95
10852	-	+	MCB	-	-	-	3/24/95
10853	-	+	MCB	-	-	-	3/13/95

Table IV (continued)

NIH	SA	MVD	BIND	DD	ANLG	RSP	REPORT*
10854	-	+	MCB	-	-	-	4/14/95
10855	-	+	MCB	-	-	-	5/1/95
10856	-	+	MCB	-	-	-	5/1/95
10857	-	+	MCB	-	-	-	8/23/95
10860	-	+	MCB	-	-	-	8/23/95
10862	-	+	MCB	-	-	-	1/2/96
10863	-	+	MCB	-	-	-	1/2/96
10864	-	+	MCB	-	-	-	1/2/96
10865	-	+	MCB	-	-	-	1/2/96
10866	-	+	MCB	-	-		1/2/96

* Date report was submitted to CPDD Biological Coordinator. MCB = Monkey Cortex Binding

NIH 10797



Codeine-6-O-sulfate zwitterion

DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 3092 nM in the presence of 150 nM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	3.47 ± 0.40	95.9 ± 5.1		9
Naltrexone (100 nM)	35.2 ± 6.7	84.0 ± 3.6	10.2	3
ICI 174,864 (100 nM)	4.48 ± 0.21	98.6 ± 1.4	1.3	3
Nor-BNI (10 nM)	4.26 ± 0.84	97.3 ± 0.7	1.2	3

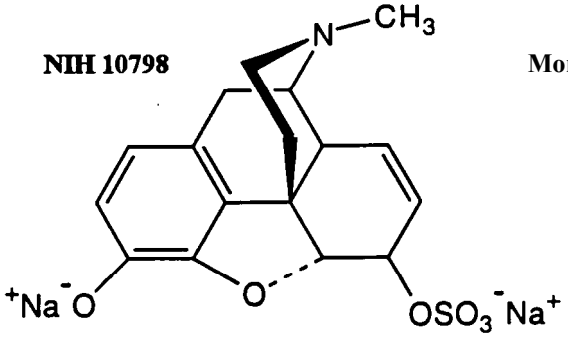
NOTE: NIH 10797 was made up at 30 mM in DMSO for this assay.

SUMMARY

NIH 10797 had slight opioid activity in the binding assay. In the mouse *vas deferens* preparation it acted as a low-potency agonist with some selectivity for μ opioid receptors.

* * *

NIH 10798



Morphine-6-O-sulfate disodium salt

DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 59.6 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	269.1 ± 84.4	80.7 ± 2.9		9
Naltrexone (100 nM)	6080.1 ± 1871.0	69.3 ± 8.1	22.6	3
ICI 174,864 (100 nM)	551.7 ± 104.2	75.4 ± 2.9	2.1	3
Nor-BNI (10 nM)	176.1 ± 29.3	83.8 ± 3.8	0.7	3

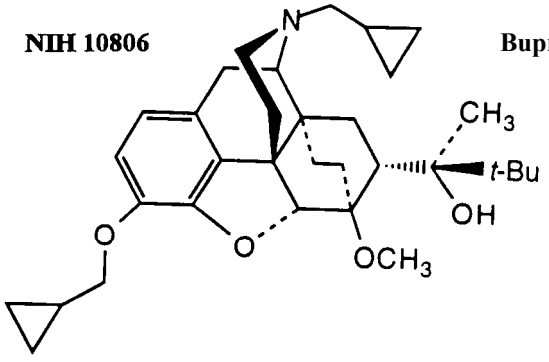
NIH 10798 (continued)

SUMMARY

NIH 10798 had opioid activity in the binding assay and, in the mouse *vas deferens* preparation, it inhibited the twitch incompletely, with some selectivity for μ opioid receptors.

* * *

NIH 10806 **Buprenorphine-3-cyclopropylmethyl ether hydrochloride**



DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 1062 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

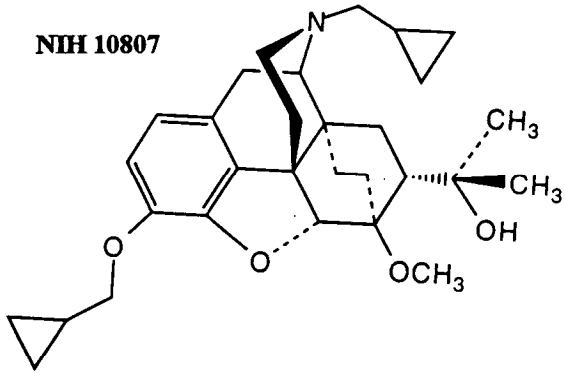
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	22.5 ± 11.6	46.4 ± 3.6		3
Naltrexone (100 nM)	3.74 ± 0.82	34.1 ± 4.4	0.2	3

Agonist	pA_2	Slope ± S.D.	pA_2 (Constrained) ± S.E.	n
Sufentanil (μ)	7.07	1.02	7.08 ± 1.41	3
DSLET (δ)	5.90	1.25	6.12 ± 0.42	3
U50,488 (κ)	SEE BELOW			

SUMMARY

NIH 10806 had low potency in the binding assay. In the *vas deferens* preparation, NIH 10806, in concentrations of 0.1 nM to 100 μM decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked by naltrexone. It is more likely that the low affinity binding in brain is associated with antagonist actions found at higher concentrations in the *vas deferens*. NIH 10806 acted as an antagonist at μ, δ, and κ receptors. The antagonism of U50,488 was insurmountable and began at a concentration of 3 μM. Although the antagonism of DSLET and sufentanil appeared to be competitive, because of the population of spare δ and μ receptors in this preparation an insurmountable antagonism might have been revealed if very high concentrations of NIH 10806 were studied. NIH 10806 was very similar to NIH 10805, but much less potent as an antagonist.

NIH 10807



Diprenorphine-3cyclopropyhnethyl ether hydrochloride

DISPLACEMENT OF [^{3}H]ETORPHINE BINDING

EC_{50} of 993 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	2.04 ± 0.25	39.5 ± 3.3		3
Naltrexone (100 nM)	1.00 ± 0.11	32.5 ± 1.8	0.5	3

SUMMARY

NIH 10807 had low potency in the binding assay. In the *vas deferens* preparation, NIH 10807, in concentrations of 0.3 nM to µM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked by naltrexone. Higher concentrations markedly increased the magnitude of the twitch. NIH 10807 acted as a very weak antagonist at µ, δ„ and κ receptors. At a concentration of 3 µM it caused a 5.1 -fold shift to the right in the sufentanil concentration-effect curve, a 2.0-fold shift to the right in the DSLET concentration-effect curve, and a 5.5-fold shift to the right in the U50,488 concentration effect curve. pA_2 values could not be determined because concentrations of 10 µM and greater of NIH 10807 markedly increased the magnitidue of the twitch.

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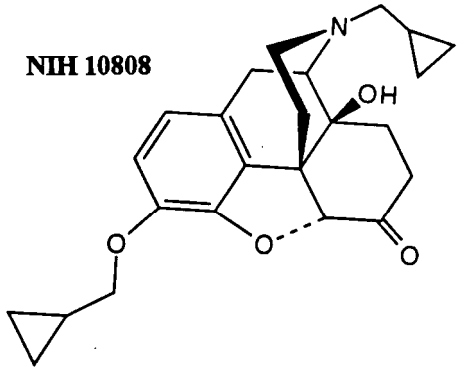
NIH 10808



Naltrexone-3-cyclopropylmethyl ether hydrochloride

DISPLACEMENT OF [^{3}H]ETOBPHINE BINDING

EC_{50} of 553 nM in the presence of 150 mM NaCl.

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	2.05 ± 1.31	32.9 ± 3.3		3
Naltrexone (100 nM)	4.14 ± 1.16	32.5 ± 1.8	2.5	3

NIH 10808 (continued)

SUMMARY

NIH 10808 had moderate opioid activity in the binding assay. In the *vas deferens* preparation, NIH 10808, in concentrations of 0.3 nM to 1 μM, decreased to some extent the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked by naltrexone. Higher concentrations markedly increased the magnitude of the twitch. NIH 10808 acted as a very weak antagonist at μ, δ, and κ receptors. At a concentration of 1 μM it caused a 5.3-fold shift to the right in the sufentanil concentration-effect curve, but no shift in the DSLET or U50,488 concentration-effect curves. pA_2 values could not be determined because concentrations of 3 μM and greater of NIH 10807 markedly increased the magnitidue of the twitch.

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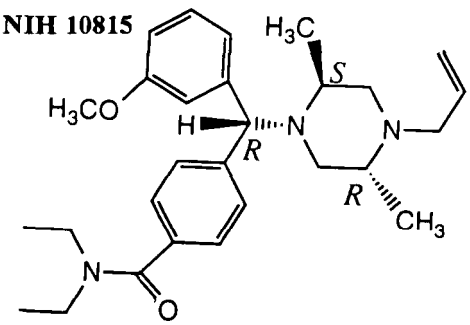
NIH 10815



(+)-4-[αR)-α-(2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide

MONKEY CORTEX BINDING (nM)

μ-receptor:	488.0
δ-receptor:	0.9
κ-receptor:	1170.0

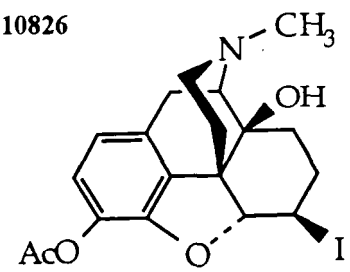
Mouse *vas deferens* and etorphine binding assay results reported in 1994 Annual Report.

SUMMARY

In the monkey cortex binding assay, NIH 10815 had significant, but low, affinity for μ and κ1 binding and its highest affinity was at the δ opioid binding site.

* * *

NIH 10826



3-Acetoxy-14-hydroxy-6β-iodo-17-methyl-4,5α-epoxymorphinan

MONKEY CORTEX BINDING (nM)

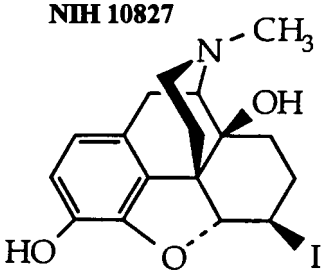
μ-receptor:	5.45
δ-receptor:	319.0
κ-receptor:	103.0

NOTE: Mouse vas deferens and etorphine binding assay results presented previously in 1995 Annual Report

SUMMARY

In the monkey cortex binding assay, NIH 10826 had significant affinity for each of the opioid binding sites with highest affinity for the μ receptor.

NIH 10827 **3,14-Dihydroxy-6ß-iodo-17-methyl-4,5 α-epoxymorphinan**



MONKEY CORTEX BINDING (nM)

μ-receptor:	0.9
δ-receptor:	50.8
κ-receptor:	13.2

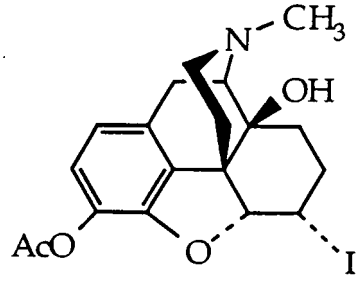
NOTE: Mouse vas deferens and etorphine binding assay results presented previously in 1995 Annual Report

SUMMARY

In the monkey cortex binding assay, NIH 10827 had significant affinity for all the opioid receptors, with the highest affinity being for the mu-opioid receptor binding site.

* * *

NIH 10831 **3-Acetoxy-14-hydroxy-6α-iodo-17-methyl-4,5α-epoxymorphinan**



MONKEY CORTEX BINDING (nM)

μ-receptor:	3.37
δ-receptor:	238.0
κ-receptor:	70.7

NOTE: Mouse vas deferens and etorphine binding assay results presented previously in 1995 Annual Report

SUMMARY

In the monkey cortex binding assay, NIH 10831 had significant affinity for each of the opioid binding sites with the highest affinity for the μ-receptor binding site.

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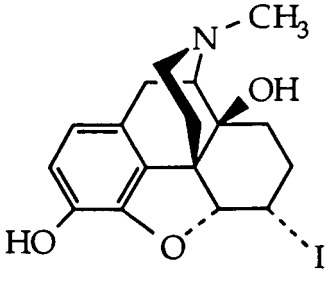
NIH 10832 **3,14-Dihydroxy-6α-iodo-17-methyl-4,5α-epoxymorphinan**



MONKEY CORTEX BINDING (nM)

μ-receptor:	1.32
δ-receptor:	78.5
κ-receptor:	14.2

NOTE: Mouse vas deferens and etorphine binding assay results presented previously in 1995 Annual Report

NIH 10832 (continued)

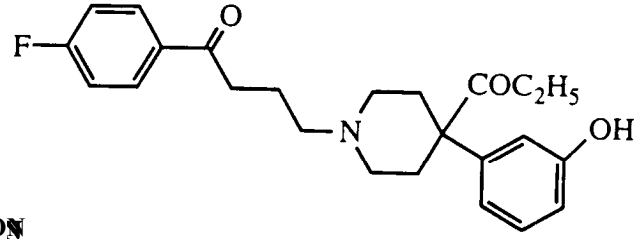
SUMMARY

NIH 10832 acted as a potent agonist in the receptor binding assay. In the monkey cortex binding assay, NIH 10832 had significant affinity for sites with the highest affinity for the μ-opioid receptor site. In the isolated, electrically-stimulated mouse *vas deferens* preparation, NIH 10832 appeared to act at μ- and δ-opioid receptors.

* * *

NIH 10834 **1-[3-(Fluorohenzoyl)propy1]-4-(3-hydroxypheny1-4-(1-oxopropyl)piperidine.HCl**

MONKEY CORTEX BINDING (nM)



μ-receptor:	19.02
δ-receptor:	179.8
κ-receptor:	448.5

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	9.79 ± 1.98	31.5 ± 2.3		3
Naltrexone (100 nM)	8.71 ± 4.23	31.2 ± 3.6	0.9	3

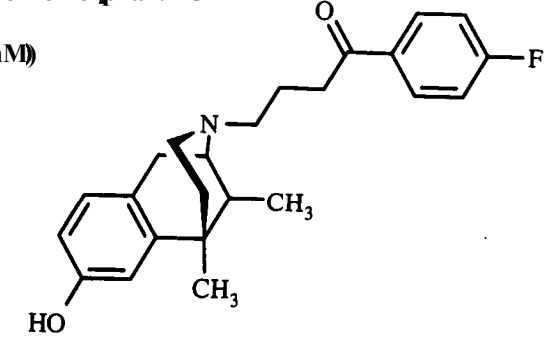
SUMMARY

NIH 10834 in concentrations ranging from 1 nM to 1 μ slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. NIH 10834, in a concentration of μM caused slight shifts to the right in the concentration-effect curves for sufentanil (5.6-fold), DSLET (3.0-fold) and U50,488 (2.0-fold). Thus, NIH 10834 appears to be a weak, nonselective opioid antagonist. In the monkey cortex binding assay, NIH 10834 was selective for the μ recognition site.

* * *

NIH 10835 **(-)-5,9α-Dimethyl-2-[3-(4-fluorohenzoyl)propyl]-2'hydroxy-6,7-benzomorphan.HCl**

MONKEY CORTEX BINDING (nM)



μ-receptor:	161.2
δ-receptor:	359.9
κ-receptor:	153.0

NIH 10835 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	1.22 ± 0.28	100.0		3
Naltrexone (100 nM)	2.34 ± 0.26	100.0	1.9	3

SUMMARY

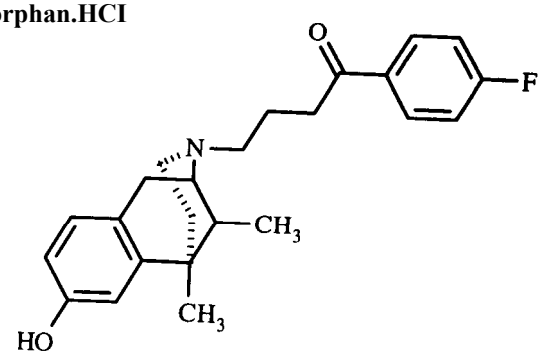
NIH 10835, in concentrations ranging from 100 nM to 100 µM decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. NIH 10835, in a concentration of 300 nM, was devoid of antagonistic activity at µ,δ,, and κ receptors. In the monkey cortex binding assay, NIH 1083 5 was of low potency.

* * *

NIH 10836 **(+)-5,9-Dimethyl-2-[3-(4-fluorobenzoyl)propyl]-2'-hydroxy-6,7-benzomorphan.HCI**

MONKEY CORTEX BINDING (nM)

µ-receptor: 105.9
δ-receptor: 9% inhibition at 6 µM
κ-receptor: 847.5



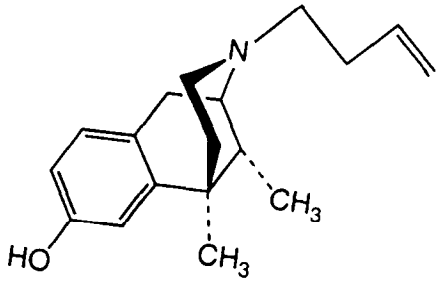
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	65.7 ± 51.7	100.0		3
Naltrexone (100 nM)	67.1 ± 46.4	100.0	1.9	3

SUMMARY

NIH 10836, in concentrations ranging from 10 µM to 100 µM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked signitlcantly by naltrexone. NIH 10836, in a concentration of 10 µM, caused slight shifts to the right in the concentration-effect curves for sufentanil (4.4-fold), DSLET (2.4-fold) and U50,488 (3.3-fold). Thus, NIH 10836 may be a very weak, nonselective opioid antagonist. In the monkey cortex binding assay, NIH 10836 was much less potent than morphine, although somewhat selective for the µ recognition site.

NIH 10847 **(-)-2-(3-Butenyl)-5,9α-dimethyl-2'-hydroxyd,7-benzomorphan.HCI**



MONKEY CORTEX BINDING (nM)

(a) μ-receptor: 3.07
(b) δ-receptor: 33.6
(c) κ-receptor: 1.52

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	102.6 ± 8.0	83.9 ± 2.1		9
Naltrexone (100 nM)	883.8 ± 8.8	80.0 ± 6.3	8.6	3
ICI-174864 (100 nM)	116.4 ± 14.0	85.2 ± 3.6	1.1	3
Nor-BNI (10 nM)	363.5 ± 100.8	85.2 ± 6.2	3.5	3

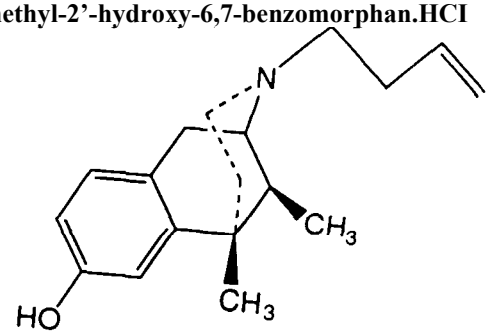
ol: 3 mM in H_xO

SUMMARY

NIH 10847, in concentrations of 10 nM to 10 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation Both naltrexone (100 nM and nor-binaltoxphimine (10 nM) shifted the NIH 10847 concentration-effect curve to the right; ICI-174864 (100 nM) did not significantly. None of the antagonists decreased maximum responses to NIH 10847. Thus, it has characteristics typical of both μ- and κ-opioid receptor agonists. In the monkey cortex binding assay, it had higher affinity for μ and κ binding sites relative to the δ site.

* * *

NIH 10848 **(+)-2-(3-Butenyl)-5,9α-dimethyl-2'-hydroxy-6,7-benzomorphan.HCI**



MONKEY CORTEX BINDING (nM)

μ-receptor: 1130
δ-receptor: 3% inhibition at 6 μM
κ-receptor: 757

MOUSE *VAS DEFERENS* PREPARATION

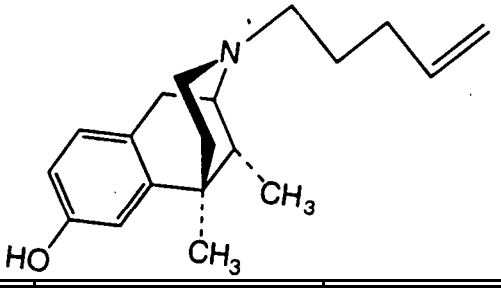
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	48.0 ± 9.0	29.5		3
Naltrexone (100 nM)	47.8 ± 10.9	27.9	1.0	3

NIH 10848 (continued)

SUMMARY

NIH 10848, in concentrations of 10 nM to 1 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas **deferens*** preparation. This response was not blocked by naltrexone. Concentrations of NIH 10848 highter than 1 μM increased the magnitude of the twitch. NIB 10848, in a concentration of 10 μM, did not shift significantly the concentration-effect curves for sufentanil, DSLET, OR U50,488. In the monkey cortex binding assay, NIH 10848 was active in displacing μ and κ ligands with quite low affinity.

NIH 10852 **(-)-5,9-Dimethyl-2'hydroxy-2-(4-pentenyl)-6,7-benzomorphan.HCI**



MONKEY CORTEX BINDING (nM)

μ-receptor: 11.86
δ-receptor: 93.41
κ-receptor: 8.37

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	536.8 ± 74.9	100.0		9
Naltrexone (100 nM)	8300.9 ± 4809.5	100.0	15.5	3
ICI-174864 (100 nM)	2029.2 ± 1158.0	100.0	3.8	3
Nor-BNI (10 nM)	973.5 ± 479.3	96.5 ± 2.5	1.8	3

Solubility: 3 mM in 20% DMSO

SUMMARY

NIH 10852 is an agonist that appears to act at μ- and δ-opioid receptors on the isolated, electrically stimulated mouse *vas deferens* preparation. In the monkey cortex binding assay, NIH 10852 had signiticant affinity for each binding site.

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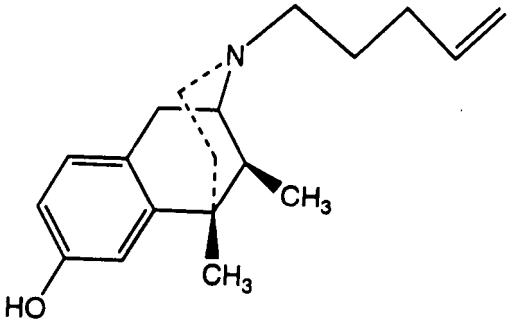
NIH 10853 **(+)-5,9α-Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-benzomorphan.HCI**



MONKEY CORTEX BINDING (nM)

μ-receptor: 40% inhibition at 6 μM
δ-receptor: 4177
κ-receptor: 0% inhibition at 6 μM

NIH 10853 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	308.4 ± 60.2	16.3 ± 3.9		3
Naltrexone (100 nM)	242.1 ± 25.0	16.0 ± 3.3	0.8	3

SUMMARY

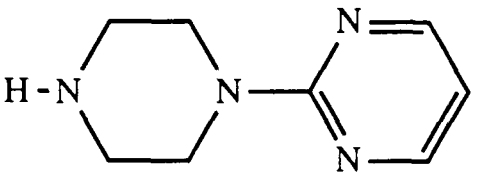
NIH 10853, in concentrations of 100 nM to 3 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. Higher concentrations increased the magnitude of the twitch. At μ and κ receptors, NIH 10853 was a very weak antagonist. At a concentration of 10 μM, it caused a 5.3-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 significant shift in the DSLET concentration effect curve. pA_2 values could not be determined because concentrations of NIH 10853 of 10 μM or greater increased the magnitude of the twitch. In the monkey cortex binding assay it had a very low potency in displacing pCl-DPDPE without significant affinity at other sites. NIH 10853 was active in both preparations, but only at close to the limit of detection in each preparation.

* * *

NIH 10854 **1-(2-Pyrimidinyl)piperazine.2HCI**

MONKEY CORTEX BINDING (nM)

μ-receptor: 6% inhibition at 6 μM
δ-receptor: 0% inhibition at 6 μM
κ-receptor: 0% inhibition at 6 μM



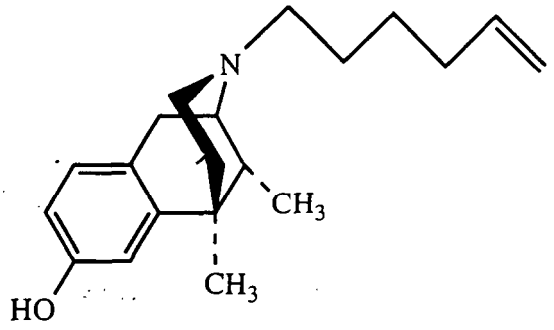
MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	515.0 ± 187.9	46.2 ± 11.2		3
Naltrexone (100 nM)	463.2 ± 108.3	47.8 ± 9.7	0.9	3

SUMMARY

NIH 10854, in concentrations of 100 nM to 30 μM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. At μ, δ, and κ receptors, NIH 10853 was devoid of antagonist activity. In the monkey cortex binding assay, NIH 10853 was also inactive.

NIH 10855 **(-)-5,9α-Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-benzomorphan.HCl**



MONKEY CORTEX BINDING (nM)

μ-receptor:	18.38
δ-receptor:	97.56
κ-receptor:	7.13

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	175.1 ± 33.2	100		9
Naltrexone (100 nM)	7904.6 ± 3808.9	100	45.1	3
ICI-174864 (100 nM)	223.9 ± 136.3	100	1.3	3
Nor-BNI (10 nM)	904.9 ± 381.9	100	5.2	3

SUMMARY

NIH 10855, in concentrations of 10 nM to 100 μM, 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 10855 concentration-effect curve to the right. Nor-binaltorphimine (10 nM, a κ opioid receptor antagonist) also shifted the NIH 10855 concentration effect curve to the right. ICI-174864 (100 nM, a δ opioid receptor antagonist) did not shift the NIH 10855 concentration-effect curve significantly. None of the antagonists decreased maximum responses to NIH 10855. Thus, in the mouse *vas deferens* preparation, NIH 10855 had all the characteristics typical of both μ- and κ-opioid receptor agonists. In the monkey cortex assay, NIH 10855 had higher affinity for κ and μ binding sites than it did for the δ site. NIH 10855 could be a mixed agonist with higher affinity for κ than for μ. Nevertheless, NIH 10855 does have some affinity for the δ receptor; it could be a δ antagonist. Our experiments have not ruled out this possibility.

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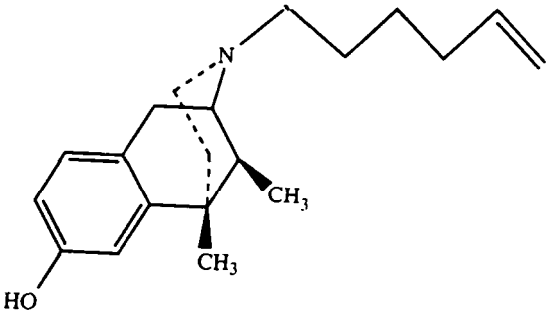
NIH 10856 **(+)-5,9α-Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-benzomorphan.HCl**



MONKEY CORTEX BINDING (nM)

(a)	μ-receptor:	816.3
(b)	δ-receptor:	6% inhibition at 6 μM
(c)	κ-receptor:	491.6

NIH 10856 (continued)

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	82.8 ± 32.4	40.2 ± 6.6		3
Naltrexone (100 nM)	52.0 ± 15.2	35.8 ± 2.7	0.6	3

Studied with NIH 10856 made up at 3 mM in 17% DMSO.

SUMMARY

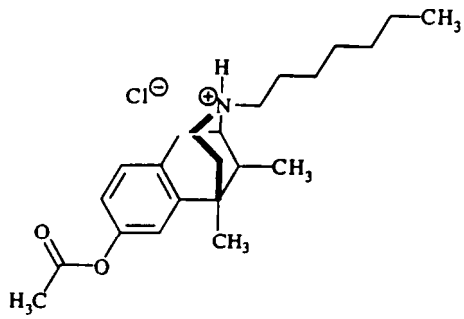
NIH 10856, in concentrations of 10 nM to 3 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked significantly by naltrexone. High concentrations markedly increased the magnitude of the twitch. NIH 10856 was devoid of significant antagonist activity at μ, κ, and δ opioid receptors. In the monkey cortex assay, NIH 10856 had low affinity for the μ and κ ligand binding sites and even lower affinity for the δ binding site. NIH 10856 has no significant opioid activity in these assays.

* * *

NIH 10857 **(-)-2'-Acetoxy-5,9α-dimethyl-2-heptyl-6,7-benzomorphan.HCI**

MONKEY CORTEX BINDING (nM)

μ-receptor: 48.6
δ-receptor: 92.7
κ-receptor: 60.0



MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	246.4 ± 55.2	93.7 ± 4.2		9
Naltrexone (100 nM)	83.7 ± 58.2	25.7 ± 6.3	0.3	3
ICI-174864 (100 nM)	96.6 ± 38.7	56.9 ± 12.5	0.4	3
Nor-BNI (10 nM)	178.4 ± 25.6	58.3 ± 1.8	0.7	3

SOL: 3 mM in 19% DMSO

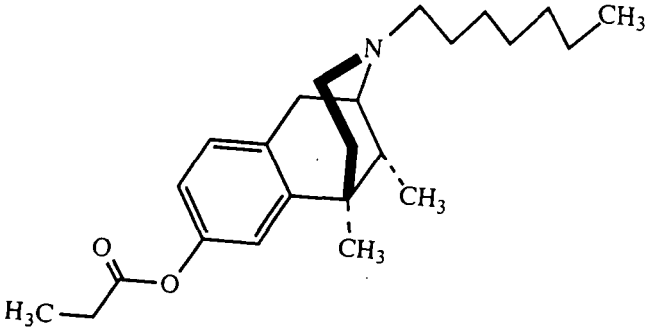
NIH 10857(continued)

SUMMARY

NIH 10857, in concentrations of 10 nM to 3 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. At no concentration did NIH 10857 completely suppress the twitch. Naltrexone (a μ opioid receptor antagonist), nor-binaltorphimine (a κ-opioid receptor antagonist), and ICI-174864 (a δ-opioid receptor antagonist) decreased the maximum response to NIH 10857, but did not shift its concentration-effect curve to the right. Thus, in the mouse *vas deferens* preparation, NIH 10857 is a very unusual agonist with respect to its interaction with naltrexone, nor-BNI and ICI-174864. In the monkey cortex binding assay, NIH 10857 had moderate affinities for each of the binding sites. NIH 10857 has an unusual profile of actions in these preparations.

* * *

NIH 10860 **(-)-5,9α-Dimethyl-2-heptyl-2-propionoxy-6,7-benzomorphan.HCl**



MONKEY CORTEX BINDING (nM)

μ-receptor: 28.2
δ-receptor: 47.0
κ-receptor: 47.5

MOUSE *VAS DEFERENS* PREPARATION

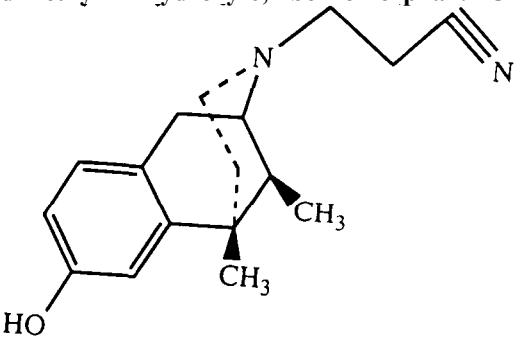
Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	194.1 ± 21.1	86.1 ± 3.3		9
Naltrexone (100 nM)	44.3 ± 7.2	19.9 ± 2.9	0.2	3
ICI-174864 (100 nM)	171.3 ± 15.5	77.7 ± 11.9	0.9	3
Nor-BNI (10 nM)	149.5 ± 13.5	86.7 ± 6.7	0.8	3

SOL: 3 mM in 19% DMSO

SUMMARY

NIH 10860, in concentrations of 10 nM to 3 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. At no concentration did NIH 10860 completely suppress the twitch. Naltrexone (a μ opioid receptor antagonist) markedly decreased the maximum response to NIH 10860, but did not shifl the concentration-effect curve to the right. Neither nor-BNI (a κ opioid receptor antagonist) nor ICI- 174864 (100 nM, a δ opioid receptor antagonist) altered the NIH 10860 concentration-effect curve significantly. None of the antagonists decreased maximum responses to NIH 10860. Thus, in the mouse *vas deferens* preparation, NIH 10860 was a very unusual agonist with respect to its interaction with the antagonists. In the monkey cortex assay, NIH 10860 had signiticant affinities for each of the binding sites.

NIH 10862 **(+)-2-(2-Cyanoethyl)-5,9α-dimethy1-2'-hydroxy-6,7-benzomorphan.HCl**



MONKEY CORTEX BINDING (nM)

μ-receptor: 40% inhibition at 6 μM
δ-receptor: 10% inhibition at 6 μM
κ-receptor: 223

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	3.96 ± 1.45	41.0 ± 8.0		3
Naltrexone (100 nM)	6.87 ± 3.47	27.9 ± 5.9	1.7	3

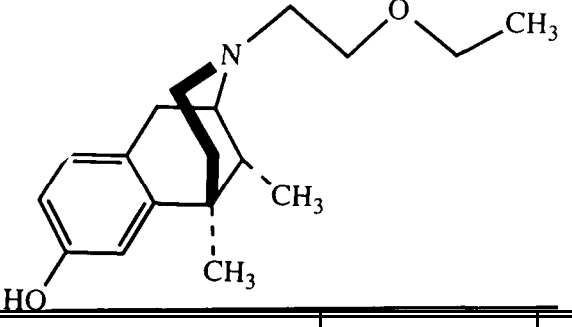
SOL: 3 mM in H_2O

SUMMARY

NIH 10862, in concentrations of 300 nM to 30 μM, slightly decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation. This response was not blocked by naltrexone. NIH 10862, at a concentration of 100 nM, was devoid of significant antagonist activity at μ, κ and δ-opioid receptors. In the monkey cortex assay, NIH 10862 had low affinity for the, and insignificant affinity for the other two sites. NIH 10862 is not likely to have significant opioid activity *in vivo.*

* * *

NIH 10863 **(-)-5,9α-Dimethyl-2-(2-ethoxyethyl)-2,'-hydroxy-6,7-benzomorphan.oxalate**



MONKEY CORTEX BINDING (nM)

μ-receptor: 4.15
δ-receptor: 115
κ-receptor: 2.56

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Maximum Response (%)	Shift (x-fold)	n
Control	209.6 ± 32.5	90.5 ± 2.3		9
Naltrexone (100 nM)	974.2 ± 243.8	76.0 ± 0.9	11.6	3
ICI-174864 (100 nM)	35.2 ± 4.3	96.7 ± 1.3	0.7	3
Nor-BNI (10 nM)	78.8 ± 14.1	78.3 ± 1.5	2.8	3

SOL: 3 mM in 50% ethanol

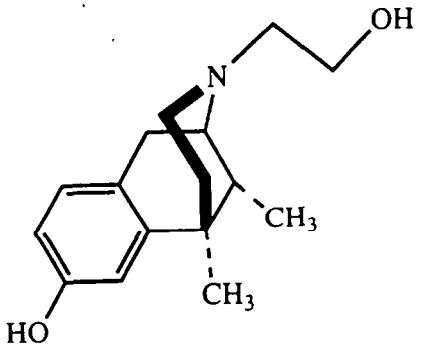
NIH 10863 (continued)

SUMMARY

NIH 10863, in concentrations of 30 nM to 30 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation Naltrexone (a μ-opioid receptor antagonist) shifted the NIH 10863 concentration-effect curve to the right. Neither nor-binaltorphimine (aκ-opioid receptor antagonist) nor ICI- 174864 (aδ-opioid receptor antagonist) shifted the NIH 10863 concentration-effect curve significantly. NIH 10863 had characteristics typical of a μ-opioid receptor agonist in the mouse *vas deferens* preparation. In the monkey cortex binding assay, the compound had signiticant affinity at each recognition site. It had highest affinity for μ andκ sites. Clearly, the preparations are not yielding congruent results for NIH 10863.

* * *

NIH 10864 **(-)-5,9α-Dimethyl-2-(2-ethoxyethyl)-2'-hydroxy-6,7-benzomorphan .oxalate**



MONKEY CORTEX BINDING (nM)

μ-receptor: 40.9
δ-receptor: 316
κ-receptor: 15.9

MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (μM)	Maximum Response (%)	Shift (x-fold)	n
Control	1.29 ± 0.30	67.6 ± 3.5		9
Naltrexone (100 nM)	2.16 ± 0.49	62.1 ± 4.2	1.7	3
ICI-174864 (100 nM)	3.71 ± 1.17	57.3 ± 3.7	2.9	3
Nor-BNI (10 nM)	0.98 ± 0.16	52.7 ± 9.9	0.8	3

SOL: 3 mM in 50% ethanol

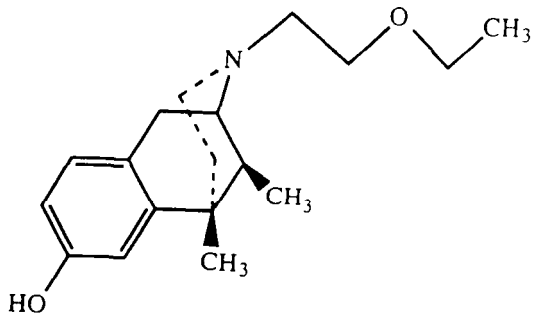
SUMMARY

NIH 10864 acted as a weak agonist at δ-opioid receptors in the mouse *vas deferens* preparation In the monkey cortex binding assay, it had affinity for each of the binding sites, although the lowest affinity was the δ receptor site labeled by pCL-DPDPE.

NIH 10866 **(+)-59α-Dimethyl-2-(2-ethoxyethyl)-2'-hydroxy-6,7-benzomorpban.oxalate**

MONKEY CORTEX BINDING (nM)

μ-receptor: 956
δ-receptor: 10% inhibition at 6 μM
κ-receptor: 629



MOUSE *VAS DEFERENS* PREPARATION

Condition	EC_{50} (nM)	Max. Response (%)	Shift (x-fold)	n
Control	101.9 ± 28.2	26.0 ± 2.8		3
Naltrexone (100 nM)	118.1 ± 21.5	24.3 ± 3.1	1.2	3

SOL: 3 mM in 50% ethanol

SUMMARY

NIH 10866, in concentrations of 30 nM to 10 μM, decreased the magnitude of the twitch of the electrically stimulated mouse *vas deferens* preparation; the NIH concentration-effect curve was not blocked by naltrexone. NIH 10866 acted as a weak antagonist at μ and κ receptors. In the presence of NIH 10866,30 μM, there was a 4.9-fold shift to the right in the sufentanil concentration-effect curve, and a 12.7-fold shift to the right in the U50,488 concentration-effect curve. NIH 10866 did not shift the ICI 174864 concentration-effect curve at any concentration. Thus, in this preparation, the drug was more potent as an antagonist at κ-opioid receptors than at μ-opioid receptors. In the monkey cortex binding assay, it was weakly active in both the μ receptor and κ receptor assays.

REFERENCES

Bertalmio, A.J.; Herling, S.; Hampton, R.Y.; Winger, G.; and Woods, J.H. A procedure for rapid evaluation of the discriminative stimulus effects of drugs. ***J Pharmacol Meth*** 7:289-299, 1982.

Carter, B.D. and Medzihradsky, F. Opioid signal transduction in intact and fragmented SH-SY5Y neural cells. ***J Neurochem*** 58:1611-1619, 1992.

Clark, M.J.; Carter, B.D.; and Medzihradsky, F. Selectivity of ligand binding to opioid receptors in brain membranes from the rat, monkey and guinea pig. ***Eur J Pharmacol*** 148:343-351,1988.

Clark, M.J. and Medzihradsky, F. Coupling of multiple opioid receptors to GTPase following selective receptor alkylation in brain membranes. ***Neuropharmacol*** 26:1763-1770,1987.

Dykstra, L.A. and Woods, J.H. A tail withdrawal procedure for assessing analgesic activity in rhesus monkeys. ***J Pharmacol Meth*** 15:263-269, 1986.

Emmerson P.J.; Liu, M-R; Woods, J.H; and Medzihradsky, F. Binding affinity and selectivity of opioids at mu, delta and kappa receptors in monkey brain membranes. ***J. Pharmacol Exp. Ther.*** 271:1630-1637,1994.

France, C.P. and Woods, J.H. Discriminative stimulus effects of naltrexone in morphine-treated rhesus monkeys. ***J Pharmacol Exp Ther*** 250:937-943,1989.

France, C.P.; de Costa, B.R.; Jacobson, A.E.; Rice, K.C.; and Woods, J.H. Apparent affinity of opioid antagonists in morphine-treated rhesus monkeys discriminating between saline and naltrexone. ***J Pharmacol Exp Ther*** 252:600-604,1990.

France, C.P. and Woods, J.H. Respiratory effects of receptor-selective opioids in rhesus monkeys. In: Quirion, R., Jbamandas, K. and Gianoulakis, C. (Eds.), ***Progress in Clinical and Biological Research: The International Narcotics Research Conference (INRC) '89,*** Vol. 328. Alan R. Liss, Inc.: New York, pp. 295-298, 1990.

Howell, L.L.; Bergman J.; and Morse, W.H Effects of levorphanol and several x-selective opioids on respiration and behavior in rhesus monkeys. ***J Pharmacol Exp Ther*** 245:364-372,1988.

Medzihradsky, F. Novel biochemical determinants in the preclinical evaluation of opiates. ***NIDA Res Monogr*** 76:349-355,1987.

Medzihradsky, F.; Emmerson, P.J; and Mousigian, C.A. Lipophilicity of opioids determined by a novel micromethod. ***J Pharmacol Meth*** 27:67-69,1992.

Medzihradsky, F.; Dahlstrom, P.J.; Woods, J.H.; Fischel, S.V.; and Mitsos, S.E. Resolution in the receptor binding of putative μ and κ opiates. ***Life Sci*** 34:2129-2138,1984.

Perrine, T.D.; Atwell, L.; Tice, I.B.; Jacobson, A.E.; and May, E.L.. Analgesic activity as determined by the Nilsen method. ***J Pharm Sci*** 61:86-88,1972.

Solomon, R.E.; Herling, S.; Domino, E.F.; and Woods, J.H. Discriminative stimulus effects of N-substituted analogs of phencyclidine in rhesus monkeys. ***Neuropharmacol*** 21:1329-1336,1982.

Smith, C.B. New approaches to the evaluation of opioid agonists and antagonists upon the mouse vas deferens preparation. ***NIDA Res Monogr*** 76:288-294,1986.

Smith, C.B.; Medzihradsky, F.; Hollingsworth, P.J.; DeCosta, B.; Rice, K.C.; and Woods, J.H. Nor-binaltorphimine is a reversible, noncompetitive opioid antagonist in the mouse *vas deferens* with high affinity for receptors in monkey brain membranes. In: Quirion, R.; Jhamandas, K.; and Gianoulakis. C. eds., ***The International Narcotics Research Conference (INRC) '89.*** A.R. Liss, Inc., pp. 65-68, 1989.

Winger, G.; Palmer, R.K.; and Woods, J.H.: Drug-reinforced responding: rapid determination of dose-response ***functions. Drug and Alc Depend*** 24:135-142,1989.

Woods, J.H.; Smith, C.B; Medzihradsky, F.; and Swain, H.H. Preclinical testing of new analgesic drugs. In: Beers, F.R, Jr. and Basset, E.G. eds. ***Mechanisms of Pain and Analgesic Compounds.*** New York: Raven Press, pp. 429-445,1979.

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