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Testing for Abuse Liability of Drugs in Humans

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Testing for Abuse Liability of Drugs in Humans

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Testing for Abuse Liability of Drugs in Humans

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FOREWARD

Ladies and Gentlemen:

I take great pleasure in welcoming you to this important conference on Testing for Abuse Liability of Drugs in Humans. I thank you all for coming and participating in the conference. This unique conference is sponsored by the Committee on Problems of Drug Dependence (CPDD), the Drug Enforcement Administration (DEA), the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA). I encourage you to participate in the discussions.

Speaking for CPDD, we are delighted to be co-sponsoring this conference with these governmental agencies. This partnership between the public and private sector is essential if we are going to solve the multiple problems associated with the abuse of chemical substances.

There are a number of people to thank for organizing this excellent meeting. First and foremost, I thank Drs. Marian W. Fischman and Nancy K. Mello, who served as co-chairs of the committee who prepared the scientific program and other aspects of the meeting. They, and each member of the human testing committee of CPDD are to be congratulated for putting together such an excellent meeting.

A debt of gratitude is also owed to Dr. Martin W. Adler, the executive officer of CPDD and his fine staff who handled all of the logistical aspects of the meeting. Finally, on behalf of CPDD, I thank the government agencies who are sponsoring this conference with CPDD for all aspects of their support. Their participation in the planning of the conference was essential. Let me hasten to add our thanks to those pharmaceutical companies who have supported CPDD financially this year. Your generous contributions have been used to support this conference and other work of CPDD.

I want to spend just a few minutes talking about what CPDD is doing at the present time and why this conference is such a vital portion of that endeavor.

The major tenet of the CPDD today is the same as it has been throughout its 60 years of existence. That is, the problems caused by drug dependence and drug abuse will be alleviated only by the appropriate use of knowledge generated from research. Clearly this includes all aspects of treatment, prevention, clinical, basic and many types of research.

The three specific objectives of CPDD are: 1) the testing of the dependence liability of drugs, 2) holding the best and most comprehensive scientific meetings on this topic, and 3) serving in advisory and other cooperative capacities with governmental agencies who also are concerned with the abuse of chemical substances. This conference addresses each of these specific objectives.

Testing for abuse potential and physical dependence liability

CPDD initiated its activity in the testing of dependence liability of chemical substances about 50 years ago when it set up the monkey colony at the University of Michigan. When the number of compounds exceeded the facility at that institution, a second colony was established at the Medical College of Virginia of Virginia Commonwealth University. Initially, both of these colonies were supported only by the generous contributions of the pharmaceutical industry. In recent years, as research has become more expensive, additional funding from NIDA was necessary to continue these tests in monkeys and to expand the testing to include other species and other procedures.

CPDD has now responded to the need to expand its animal physical dependence liability testing capabilities to include abused substances other than opiates. Due to the excellent work of Dr. Theodore J. Cicero and the drug testing committee, CPDD has established procedures to test drugs of the stimulant or depressant type for their dependence liability. The University of Chicago and Johns Hopkins University have joined the other two institutions in carrying out these evaluations. Many standard compounds were run through this elaborate testing profile and at this time six compounds submitted from industry are being tested on a blind basis. CPDD will serve as an “honest broker” for these tests as we have for years for the testing of opioids.

The reason for initiating this meeting is to help us in our next phase of testing compounds for dependence liability. We feel that CPDD should

develop methodologies for testing the abuse potential of compounds in humans. Our subcommittee on human testing realized that such a meeting was an essential step in our initiation of this important phase of testing.

The second objective of CPDD is to sponsor important scientific meetings in the area of drugs of abuse. The format of the annual meeting has been changed to include symposia, plenary Lectures, and an increased number of poster presentations. The publication of the proceedings of the meetings is also being improved on a continual basis.

Although these changes did not receive unanimous support from all members of CPDD, even the most doubtful members will not argue with the excellence of the science at the last two meetings. This will continue for the 1989 meeting in June. CPDD also has sponsored other meetings including the Narcotic Agonist/Antagonist meeting in Innisbrook, Florida in 1983, and a conference on Cocaine in 1986. This meeting on human testing is a continuation of that activity.

The third objective of CPDD is to interact with governmental agencies at the state, federal and international level. This takes many forms. For each of the last two years, CPDD has testified before the appropriations committees in both Houses of Congress for continued and increased support for research in this important area. We feel that increased federal funding for research helps researchers in academia, government and industrial laboratories. On numerous other occasions, CPDD has met with key congressional leaders and their staff. CPDD has tested numerous compounds, written extensive review type reports, and sent representatives to the World Health Organization meeting in recent years.

Although it is not a governmental agency, CPDD will meet with the executive officer of AALAC, the accrediting group for laboratory animals, with the objective of having CPDD representation on the Advisory Board. This type of interaction is essential in the continuing battle against those who are against the humane use of animals in research. The above is not an exhaustive list of what CPDD is doing with governmental and other agencies, but time does not allow me to mention them all.

The best example of how CPDD is interacting with various governmental agencies is this conference. I welcome you to it, I thank you for coming and contributing to this important topic.

WILLIAM L. DEWEY, Ph.D.

Chairman, CPDD

Preface

The Committee on Problems of Drug Dependence (CPDD) was established in 1929, and is the oldest organization in the United States concerned with the scientific study of drug dependence and drug abuse. The CPDD has traditionally supported independent research laboratories to evaluate opioids for abuse liability and dependence potential using established methodologies in non-human research subjects. CPDD has also supported research to identify compounds with opioid antagonist or agonist-antagonist properties. More recently, similar standardized and objective procedures have been used to study stimulants and depressants in non-human research subjects. It is now well established that primates will self-administer most drugs that are abused by man and are a valuable model for drug abuse liability testing.

After over half a century as a forum for the investigation and evaluation of the effects of drugs of abuse, in 1983, the CPDD, under the leadership of Dr. Joseph V. Brady, began to explore the possibility of extending its program of pre-clinical drug testing and evaluation to human research subjects. Dr. Charles O'Brien volunteered to chair a subcommittee on Human Testing, and representatives of academia, industry and government began to discuss strategies for implementation of a human testing program. By 1985, with Dr. Mary Jeanne Kreek as chairperson of the CPDD and Dr. Marian W. Fischman chairing the Human Testing Subcommittee, this new initiative had assembled a network of investigators experienced in drug assessment in humans. The long and continuing process of identifying appropriate procedures, subject populations, and databases which might be useful for evaluation of abuse liability and dependence potential in humans had begun. Working toward this goal, the Human Testing Subcommittee has determined that both outpatient testing facilities and specialized inpatient research wards are available for drug abuse liability and dependence potential studies. In many cases, drug abuse

liability can be evaluated concurrently with other safety and efficacy measures. Standard self-report measures of drug effects can be extended to include measures of learning and performance, autonomic responses, drug preferences and motivational changes. Of course, all studies conducted with human volunteers must be carried out in accordance with the requirements of local Institutional Review Boards.

Currently, the involvement of the CPDD in the Human Testing Program is mainly one of coordination. CPDD helps to identify the drugs to be tested and supports the validation of established methodologies using standard compounds to encourage cross-laboratory generality of test procedures. In addition, the Committee consults on the development of protocols appropriate for specific drugs, and functions in an advisory capacity for those organizations requesting assistance. Finally, CPDD maintains a directory of investigators experienced in research on abuse liability and dependence potential testing in human research subjects.

In November 1988, the Committee on Problems of Drug Dependence, in conjunction with the National Institute on Drug Abuse, the Food and Drug Administration and the Drug Enforcement Administration sponsored its first conference on Testing for Abuse Liability of Drugs in Humans. This conference was organized by CPDD Human Testing Committee co-chairs, Dr. Marian W. Fischman and Dr. Nancy K. Mello, with the assistance of a planning committee consisting of Dr. Roland R. Griffiths, Dr. Herbert D. Kleber, Dr. Jack H. Mendelson, and Dr. Edward C. Senay. The main purpose of this conference was to disseminate information about the methodologies now available for testing drugs in humans, the range of data that can be obtained, and the conclusions about abuse liability and dependence potential that can be drawn from such data. Contributors were asked to critically assess current methods for evaluating drugs in human subjects and to describe both the advantages and limitations of each approach. This information permits identification of areas in which further research and development are needed.

Approximately 80 representatives from industry, academia and government gathered to discuss these issues and the results of this seminal conference on human drug testing are included in this monograph. This effort has been facilitated by the good working relationship among federal government agencies, academic institutions involved in drug development and research, and the pharmaceutical industry. The mutual interests of these various groups have best been served through close professional interactions, and the ultimate success of the CPDD drug testing initiative with humans will require continued collaboration and cooperation. We hope that this is just the first of a series of CPDD sponsored conferences

designed to analyze specific issues related to testingfordrug abuse liability and dependence potential. The CPDD is committed to stimulating and maintaining a dialog among the various organizations actively involved in drug development, drug regulation and research on drug dependence and drug abuse.

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CHAPTER 1

Testing and Abuse Liability of Drugs in Humans

Charles R. Schuster, Ph.D.

INTRODUCTION

I am very pleased to be able to participate in this conference. Until I became the Director of NIDA, a great deal of my professional life was devoted to the development of procedures to test the dependence potential and abuse liability of drugs. (Schuster and Thompson 1969; Schuster and Johanson, 1974; Schuster and Balster 1977; Woolverton and Schuster 1983). So, I come here not only as an interested government official and as one of the co-sponsors of this meeting, but also as a scientist with a great interest in this area.

The recently enacted 1988 Anti-Drug Abuse Act contains significant new funds for NIDA research and specifically earmarks $10 million for the area of drug development. Drug development refers not only to the development of drugs to be used in the treatment of addiction to illicit drugs, but also to the development of drugs that will satisfy medical needs, yet will possess lower abuse liability and dependence potential than do currently existing therapeutic drugs. We are very pleased to add the $10 million to our already existing program of drug development, and we look forward to the major advances in this area that this funding will make possible. However, we need some help from industry as well as from the laboratories who do abuse liability testing. From NIDA's point of view, the abuse liability program fits into two areas. It is both basic research and prevention. With regard to the latter, it is obvious that preventing drugs with high abuse liability from falling into the hands of those who would abuse them is really primary prevention. To do this, it is not necessarily the case that drugs with high abuse liability must be kept off the market. Rather, their introduction into the market should be made with full knowledge of their abuse potential and the assignment of appropriate regulatory conditions. No less important is the basic research aspect of abuse liability testing. Obviously, the opportunity to test many, many drugs which differ in chemical structure and pharmacologic action and to correlate these measures of dependence and abuse liability provides insight into the basic mechanisms underlying these drug actions. Basic

science is also well served by these activities because understanding the basic behavioral and biological mechanisms underlying dependence will enhance our understanding of the neurobiology of mood and affect.

I was going to discuss briefly the history of the Committee on Problems of Drug Dependence (CPDD) but fortunately that has already been covered by others. You are all aware of the fact that CPDD has had an extensive history in evaluation of drug dependence potential. I would recommend that you read Nathan B. Eddy's book (1973) which reviews this history if you have not already done so. I took advantage of the opportunity to come here today and reread that book, and I can say that I have learned a lot from it. One incident that I have to mention concerns Drs. Small and Eddy's "grooming" of Dr. Himmelsbach to take charge of the research activities at the Lexington Narcotics Farm. Dr. Himmelsbach, then a young commissioned officer in the Public Health Service, was first sent to work with Dr. Toraid Stollmann at Western Reserve University in the development of a rat model of morphine addiction. Later, he was sent to Michigan to study under Dr. Eddy to gain experience in controlled pharmacological testing and training in the appropriate "research attitude." As I look around the audience today, I am pleased to see the number of people who essentially had the same kind of rigorous science training in an animal laboratory and then applied these same kinds of procedures, philosophy, and experimental designs to the problem with which we are dealing today, that is, the assessment of abuse liability in humans. Obviously, a pattern of training that Dr. Eddy initiated has been found to serve us well.

Dr. Eddy's review of CPDD's program to develop dependence free analgesics is interesting also. The rationale for the search for dependence free analgesic drugs under the Advisory Committee on Drug Addiction of the National Research Council of 1929 rested on two points. Information indicated that codeine was an effective analgesic with little addiction liability compared to morphine. This suggested that other chemical modifications of morphine might result in even less abuse liability. In addition, a temporal correlation between the introduction of procaine onto the market and a large decrease in the widespread abuse of cocaine suggested that, should a synthetic substitute for morphine be found, morphine addiction would also decrease. We now know that the description of codeine's abuse liability was based upon testing an inadequate dose range and that the availability of synthetic replacements for cocaine did not preclude the emergence of cocaine addiction at epidemic rates in the 1970s. Nonetheless, these two observations, according to Dr. Eddy, lead the NRC Committee on Drug Addiction to pursue the goal of finding a dependence free analgesic.

GOALS OF ABUSE LIABILITY TESTING

Iatrogenic Addiction and Dependence

I would ask the question again, why should we evaluate drugs for their abuse liability or their dependence potential? Obviously, one reason relates to the basic science goals that are served by abuse liability testing which I have already mentioned. In addition, there are two practical reasons: (1) to avoid iatrogenic addiction and dependence, and (2) to restrict the availability of new drugs for rediversion into the drug subculture. However, is our level of concern about iatrogenic addiction or dependence appropriate? Consider the work of Porter and Jick who reported that an analysis of over 39,000 hospital records identified 11,382 hospitalized patients who had been treated with various narcotics. Follow up on these people over a period of 5 years or longer revealed only four cases of iatrogenic addiction (Porter and Jick 1980). Clearly, fear of iatrogenic addiction does not justify either the under-utilization or the avoidance of the use of dependence-producing drugs for the treatment of patients' pain since iatrogenic addiction, at least in this study of patients given these drugs in a hospital setting, was extremely low.

Amphetamines: Another drug that we associate with abuse but for which there is little evidence of iatrogenic dependence is amphetamine. The first studies that I ask you to consider are old and come from Chauncey Leake's book (1958). At the time when it was written in 1958, he cited several clinical studies in which amphetamines were given daily for years with no sign of habituation or dependence. One hundred seventy-five patients were exposed to 25 mg a day of amphetamine for four years for therapeutic purposes and showed no signs of habituation or addiction. Other studies of doses of up to 45 mg a day used for at least nine months concluded that there was no evidence of habituation or iatrogenic addiction in these patients (Leake 1958). More recently, several members in the audience such as Drs. Bigelow and Griffiths (1980) allowed patients, who were being treated for obesity, to take as many as six 5 mg *d*-amphetamine tablets per day. They followed drug consumption over a period of four weeks. The total number of amphetamine tablets that were available over the four week period was 168, yet people averaged only 1.8 to 1.9 tablets a day, a fraction of the number available. Our assumption would be that if these people had become dependent we would have seen an increase in their consumption of the drug and, in fact, over the 4 week period, the number of tablets taken each day was never more than half those available and went down over time. I think that the potential for iatrogenic dependence on opiates and amphetamines when they are used under appropriate circumstances is less than we might realize.

Benzodiazepines: Many people have concluded that iatrogenic dependence to benzodiazepines is possible even at therapeutic doses. These data are complex, and I will not attempt to review them here. Nevertheless, I would say that given the numbers of people who have been exposed to the benzodiazepines, the incidence of iatrogenic dependence is still relatively low. While testing for dependence potential in order to avoid iatrogenic addiction is obviously of importance, I think we should not overstress it since the incidence of iatrogenic dependence and addiction at least with narcotics and amphetamines appears to be low.

Restriction of Drug Availability

The second reason we do abuse liability testing is because we want to restrict the availability of drugs to appropriate patients and not let them get into the hands of the drug using subculture. Rediversion of drugs should concern us for several reasons. For example, physicians and pharmacists are concerned about stocking and storing drugs that have high abuse liability and dependence potential because of potential theft and robbery. There are many drug stores that will not stock narcotics for this reason. However, regulations that decrease the opportunity for drug diversion may also increase cost and decrease availability to patients. Furthermore, the use of a drug that is scheduled because of its dependence potential or addiction liability may stigmatize patients who have to take it. I have seen an illustration of this where an individual was taking pentazocine and getting effective pain relief. The family became concemed that the patient might become addicted when they found out that pentazocine was being combined with an antihistamine and administered intravenously in the drug subculture. This type of stigmatization could be avoided if we had an analgesic that was free of abuse liability. Not only would such a drug do a great deal to decrease illicit use, but more importantly, it would allow patients pain control without stigmatization,

IMPORTANCE OF DEFINING POPULATIONS FOR TESTING

The various applications of abuse liability testing require researchers to consider the nature of the population represented in their studies and the nature of the population to whom the results can be applied. If researchers are interested in iatrogenic addiction, then they should be testing drugs in the appropriate patient population because this is the group who will be exposed therapeutically. You cannot use the members of the drug using subculture and find that they will use the drug and then assume that patients will become dependent on the drug. On the other hand, if you are interested in whether or not the drug, if it were available, would be used

by the drug using subculture, then obviously you want to go to abusers of similar drugs to carry out your studies. Thus, for example, if you are interested in whether anew benzodiazepine has more or less abuse liability than those currently available, you should test it in people who are currently misusing benzodiazepines.

If you want to study the issue of vulnerability to drug abuse, i.e., are there characteristics about people that make them more or less susceptible to the reinforcing or abuse potential of drugs, then you would have to have a heterogeneous population. In many instances, we use a normal population to determine those who do and do not find the drug sufficiently reinforcing to continue to use or abuse it. In any case, the nature of your question and the application you wish to make of your answer should determine the nature of your subject population.

FACTORS CONTRIBUTING TO RATES OF DRUG ABUSE IN THE GENERAL POPULATION

The final thing I want to talk about is the issue of what variables or factors modulate whether or not abuse liability is actually realized. Animal and human screening procedures have identified dozens of narcotics that appear to have high abuse liability, yet there is relatively little abuse of them. Obviously, a number of factors influence whether or not a drug will be used illicitly. One factor is potency: drugs in a laboratory can be given in large quantities, but the drug using subculture does not want to carry suitcases of the drugs around in order to get high; it is impractical. On the other hand, drugs such as the superfentanyls, which are so potent that very tiny amounts can result in lethal overdosage, are also a problem because the drug using subculture may not be equipped to do the necessary dilutions to achieve a desired effect. Solubility is another factor if a drug is going to be used intravenously. The more difficult the drug is to solubilize, the less attractive it is to street users. As we have learned from crack and cocaine, if a drug can be smoked, it has a high probability of abuse. Thus, route of administration is clearly a factor.

Environmental factors must be considered as well. Social milieus, such as those of the 60s and 70s in which drug experimentation was considered a normal part of growing up, exposed a great proportion of the population to illicit drugs. Drugs that individuals considered desirable continue to be used and abused. Other social/behavioral factors include peer pressure and the association between drug use and role models. Cost of drugs is also a factor in whether or not a drug is widely abused.

SUMMARY

In summary, there are a number of factors to be considered in abuse liability testing such as the purpose of the testing and its potential applications that determine which subject population we should employ. Furthermore, we should not expect to see a perfect correlation between abuse liability testing and the actual abuse of these drugs because there are many factors that will modulate or modify whether or not abuse liability becomes activated and the abuse of any specific drug becomes a social problem.

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CHAPTER 2

The Necessity and Utility of Abuse Liability Evaluations in Human Subjects: The FDA Perspective

Frank J. Vocci, Jr., Ph.D.

INTRODUCTION

Assessments of the abuse potential of psychoactive drugs in preclinical and clinical studies are used in regulatory decision making processes under the Controlled Substances Act (CSA) and the Federal Food, Drug, and Cosmetic Act (FD & C Act). The involvement of the Secretary of Health and Human Services in the evaluation of drugs of abuse is mandated in section 201 (b) of the CSA. Further, in the New Drug and Antibiotic (NDA) regulations (21 CFR 314.50 (d) (5) (vii)), the Food and Drug Administration (FDA) has codified the requirement for clinical studies of abuse potential and requires the pharmaceutical sponsor to submit proposals for scheduling under the CSA. However, FDA recognizes that there are drugs of abuse that will not be pursued for marketing by the pharmaceutical industry. In certain cases, the toxicological profile of a compound may preclude clinical testing (e.g., MDMA) or compounds of more limited interest may be evaluated for drug scheduling using data solely from preclinical studies (e.g., p-fluorofentanyl).

In the case of drugs that are being pursued for marketing or are amenable to study in human subjects and of scientific, medical, orregulatory interest, preclinical data may be inadequate for decisions that must be made under both the CSA and The FD&C Act. Preclinical data assessment can suggest the following conclusions: a drug can appear to have a lesser, equal, or greater abuse potential than an appropriate prototype; additionally, a drug may have an equivocal or conflicting (e.g., species-specific) profile. Further, the validity of a preclinical assessment may be reviewed on the basis of pharmacokinetic differences (rates of absorption, metabolism, excretion and "pro-drugs" which can be metabolized qualitatively and quantitatively differently) and pharmacodynamic differences (subtle shifts in receptor subpopulations across species and/or shifts in receptor selectivity) between animal and human populations. Even in the case of

valid preclinical data, there are limitations to the feasibility and interpretation of certain drugs/dosage forms and our ability to make fine discriminations in abuse potential from preclinical data.

Thus, clinical studies are needed for the following scientific reasons: to validate the conclusions of either lesser or greater abuse potential from preclinical data; to evaluate the psychopharmacology of drugs in human populations in situations where the preclinical data are equivocal or species-specific; to evaluate the onset, peak, and duration of subjective effects as a function of dose and route of administration; to relate the degree of overlap between the therapeutic dose range and the range of doses producing subjective effects; to evaluate thegeneralizability of drug timing in different human subject populations; and to evaluate the effects of drugs on inner mental life (e.g., cognitive processes including memory/amnesia, and affective changes). Clinical studies are also needed in the case of a sponsor's claim of the following: reduced or no abuse potential; reduced abuse potential by combining with an antagonist/abuse deterrent; and lack of additive or potentiative effects with alcohol.

Other situations necessitating clinical studies include when a dosage form is not amenable to study in preclinical populations (e.g., drug in chewing gum) and in the case of new drug classes (e.g., inverse benzodiazepine receptor agonists). Finally, efficacy and safety of potential agents for treatments of drug abuse/dependence must be validated in pilot clinical studies. Data generated from the types of clinical studies mentioned above can be used for CSA scheduling purposes and drug labeling issues under the FD&C Act.

FDA'S REGULATORY RESPONSIBILITIES REGARDING DRUG ABUSE

I have been asked to describe FDA's view on human abuse liability testing. But before I get into this topic, I would like to define FDA's responsibilities in the area of drug abuse. The involvement of the Secretary of Health and Human Services in the evaluation of drugs of abuse is mandated in section 201 (b) of the CSA. FDA, in concert with the National Institute on Drug Abuse (NIDA), has been given the responsibility for the assessment of abuse potential and dependence capacity of psychoactive drugs and the necessity and propriety of drug scheduling under the Controlled Substances Act (CSA). Further, in the New Drug and Antibiotic (NDA) regulations (21 CFR 314.50 (d) (5) (vii)), FDA has codified the requirement for clinical studies of abuse potential and requires the pharmaceutical sponsor to submit proposals for scheduling under the

CSA. FDA regulates the clinical investigation of drugs of abuse and products which may alter the abuse potential of a product through the Investigational New Drug (IND) process. The regulation of clinical studies includes clinical pharmacology studies which demonstrate the therapeutic utility of a drug, basic clinical research issues involved in defining the neurobiology of a drug of abuse, and studies which are aimed at defining the abuse potential of a drug. FDA also has the responsibility for the determinationof safety and efficacy of psychoactive drug products and their directions for use for drug products marketed in the U.S. Statements regarding the abuse potential of a drug and other related pharmacological properties can be found in the CLINICAL PHARMACOLOGY, WARNINGS, DRUG ABUSE AND DEPENDENCE, DRUG INTERACTIONS, and possibly DRUG OVERDOSE sections of the product labeling.

As stated above, FDA has codified the requirement for clinical studies of abuse potential for drugs developed for marketing. This requirement evolved from the general policy that the ultimate model for the determination of drug effects in man is man. This basic tenet has held across all drug classes and would be the same for drugs of abuse. In fact, the Guideline for the Format and Content of the Clinical Section of New Drug Applications states that if a sponsor does not perform (clinical) studies of abuse potential of a drug which is chemically or pharmacologically similar to a known drug of abuse, an explanation should be given as to why it was unnecessary to perform such studies.

RELATIVE CONTRIBUTIONS OF CLINICAL AND PRE-CLINICAL TESTING FOR ABUSE POTENTIAL

Since the field of drug abuse research has both preclinical and clinical studies, I would like to give you some insight into how we perceive the relative contributions of preclinical and clinical testing for the determination of abuse potential.

Preclinical studies have an important role in the determination of abuse liability of a substance. A variety of test systems are used to look for similarities and differences between a test substance and a standard. For example, radioligand binding experiments, neurochemistry experiments involving release or uptake of neurotransmitters, *in vitro* smooth muscle preparations, pharmacological studies (e.g., locomotor activity, rotarod testing, and antinociception testing), and certain toxicology studies (e.g., isolated versus aggregate lethality studies) can and are used to make inferences about the abuse potential of a drug. Additionally, behavioral

pharmacology studies are employed to define the stimulus generalization properties, the reinforcing capacity, the pattern of drug intake under various conditions, and the substitution capacity of a test drug in physical dependence paradigms. From a general toxicological standpoint, preclinical studies which define the acute lethality and subacute toxicity support the relative safety of administration of a psychoactive compound to man. It should be remembered that this is especially important in the field of drug abuse testing as the range of doses administered to volunteer populations is often several multiples of the recommended therapeutic dose range. Thus, the acute toxicity of a drug and its potential reversibility are issues that affect human drug testing in general and human abuse liability assessment in particular. Moreover, as these data are often generated before clinical studies, preclinical data are used for hypothesis generation. During the development of a drug product, preclinical studies used for hypothesis generation will support four possible outcomes. These outcomes are shown in table 1. The first possible outcome is that the abuse potential of a drug is equivalent to a prototypic agonist. In the case of obvious pharmacological equivalence the drug would not need any

Table 1. Possible outcomes from preclinical studies regarding abuse potential of a drug under development

CASE	OUTCOME
#1	Test drug is equivalent in abuse potential to a prototypic agonist
#2	Test drug has a lesser abuse potential than a prototypical agonist
#3	Test drug has a greater abuse potential than a prototypical agonist
#4	Data on test drug are conflicting with respect to abuse potential of a prototypic agonist

further testing for the determination of scheduling unless the firm developing the drug did not accept the preclinical findings. In that case, it is their prerogative to perform clinical studies that substantiate their claim of a lesser abuse potential. The second and third cases, that is involving the situations in which a drug appears to have a greater or lesser abuse potential than a prototype, should be followed up by clinical studies that test the appropriate hypothesis. The fourth case, namely where the preclinical data are equivocal or conflicting (e.g., species-specific effects),

also requires clinical studies to determine the abuse liability of the substance in man.

I will give examples of each type of possible outcome. The first situation canarisewhenanopioidagonist issubmitted to the Committee on Problems of Drug Dependence (CPDD) testing program. Academic and industry medicinal chemists continue to submit compounds for evaluation in this test system. If a substance is determined to be a full morphine-like agonist, no further testing is necessary to determine the abuse potential of the substance. A second example of this type of outcome can arise when afentanyl analog is tested. If the analog shows full agonist activity, no further testing is necessary for appropriate regulatory action.

An example of the second case, i.e., a drug with a lesser abuse potential, would be buspirone. Although all the preclinical data suggested a lack of sedative-hypnotic type activity, it should be noted that FDA asked the sponsor to conduct clinical psychopharmacological studies to substantiate the lack of reinforcing capacity (Cole et al., 1982: Griffith et al., 1986) and lack of interaction with ethanol. Also please note that two clinical studies were performed to determine and validate the lack of reinforcing subjective effects of this compound.

Anexampleof a drug withpossiblygreaterabusepotential than a prototype was suggested by the differential rate of self-administration of midazolam versus diazepam in the baboon (Griffiths et al., 198 1). In fact, midazolam response rates approached those seen with cocaine and pentobarbital. The robust self-administration of midazolam, also seen with triazolam, was suggested to be due to the rapid elimination rates of these drugs (Griffiths and Lukas 1982). The clinical abuse potential of this drug compared to diazepam is still an open issue.

The fourth type of outcome i.e., equivocal or conflicting results, can be illustrated by the data on butorphanol. In the rat, butorphanol administration occasioned responding to both a morphine-like discriminative stimulus and also to a cyclazocine stimulus (Holtzman 1985). In the spinal dog preparation, butorphanol did not suppress morphine abstinence (Martin et al., 1976). In the squirrel monkey, butorphanol partially generalized to morphine (Holtzman 1985). Butorphanol did not suppress morphine withdrawal signs in dependent rhesus monkeys undergoing withdrawal (Swain et al., 1973). However, butorphanol was self-administered in rhesus monkeys, being similar to pentazocine in this regard (Woods 1977). Thus, the preclinical data suggested a drug with both morphine-like and nonmorphine-like properties.

One possible interpretation of these data is that there are interspecies differences in the types of opioid receptor subtypes with which the drug interacts. Another possibility is that the intrinsic efficacy of the drug for each opioid subreceptor type may change from species to species. The question was whether butorphanol would be perceived to be morphine-like or more like pentazocine in man. Thus, it can be seen that conflicting or difficult to interpret preclinical data necessitate evaluation of the abuse potential of a compound in man. Administration of butorphanol to human post-addicts produced the following morphine-like effects: positive dose-response effect on opiate signs and symptoms, and subjects' liking and observers' liking scales. However, the drug also failed to produce a significant score on the Morphine-Benzedrine Group subscale. Unlike morphine, butorphanol produced dose-related increases in the Pentobarbital Chlorpromazine Alcohol General (PCAG) and Lysergic Acid Diethylamide (LSD) subscales of the Addiction Research Center Inventory (ARCI) (Jasinski et al., 1975). A follow-up study by these same investigators compared butorphanol to pentazocine, cyclazocine, and morphine. The observations of elevated scores on the LSD and PCAG subscales were confirmed for butorphanol. In this regard it was like pentazocine and cyclazocine and unlike morphine. Butorphanol, cyclazocine, and pentazocine produced a different cluster of responses than morphine on the symptoms and signs categories for "sleepy," "drunken," "nervous," and "barbiturate-like." A chronic dosing study in post-addicts noted that an 8 mg S.C. dose of butorphanol was consistently identified as a barbiturate (170/210 possible identifications). The liking scores from the chronic dosing study showed butorphanol did not produce elevated scores in liking whereas historical data from the same laboratory showed somewhat dose-related elevated liking scores for 30, 120, and 240 mg. of morphine per day (Jasinski et al., 1976). The finding of a pentazocine-like effect of butorphanol was confirmed by Preston et al. (1987), who reported that butorphanol was identified as pentazocine by post-addicts who were trained to discriminate hydromorphone from pentazocine and saline.

There are several situations in which preclinical data will suffice for the determination of the necessity of drug scheduling under the CSA. The first has already been mentioned: i.e., the case where a full agonist is shown to be equivalent in abuse potential to a prototype. Also in the case of a "street" drug, preclinical data showing a generalization to morphine, PCP, or amphetamine in concert with other pharmacological and behavioral data will suffice for drug scheduling under the CSA. In part this is because the recognition of a potential for abuse will necessitate that the drug be placed into Schedule I. Thus, a fine discrimination of abuse potential may not be necessary. Finally, it may be unethical to test a drug

of abuse in a human population due to a lack of preclinical toxicity data or a disturbing finding associated with administration of the drug in animals (e.g., MDMA). In this instance, preclinical data will suffice for the determination of drug scheduling under the CSA.

There are several considerations which must be kept in mind in the extrapolation of preclinical data to man. It must be appreciated that interpretation of preclinical data must consider biological and pharmacological differences between animal species and man. Biological differences between animals and man include a higher rate of metabolism of xenobiotic compounds in animal species. This generally produces a more rapid excretion of compounds that results in a shorter duration of action of a drug in infrahuman species. Table 2 illustrates the point about

Table 2. Diazepam terminal plasma elimination half-lives in several species

Species	Half-life(hours)
Rat	1.1
Guinea pig	2.4
Rabbit	2.7
Dog	7.6
Man	32.9

Data abstracted from Klotz et al., 1976

differences in plasma elimination half-lives for diazepam (Klotz et al., 1976). Additionally, qualitative differences in drug metabolism are possible. Subtle shifts in receptor subpopulations across species or in intrinsic efficacy of a drug towards receptor subpopulations may cause problems in data interpretation and extrapolation. For example, a drug may be a partial agonist in one species at a receptor subtype and an antagonist at the same receptor subtype in another species. Other possible differences in the estimation of abuse potential could arise in the situation of "pro-drugs"; i.e., substances which must be metabolized to active metabolitesbefore attaining pharmacological activity. If a species lacked the necessary enzymatic machinery or simply did not biotransform the substance the same as man, a significant discrepancy in the abuse potential

of the substance could result. An example of such a drug would be tilidine, an opioid agonist. The drug produced mild dependence after 47 days of administration in rats. In morphine dependent rhesus monkeys, parenterally administered tilidine did not demonstrate either agonist or antagonist properties. In man, tilidine was 1/8-1/10 as potent orally and 1/22 as potent parenterally as morphine in producing subjective effects and miosis (Jasinski and Preston 1986).

From the preceding discussion, it can be seen that one cannot possibly answer all the questions about the abuse potential of a drug from preclinical studies. Thus, clinical studies are necessary from a scientific standpoint.

Clinical evaluation of abuse potential is also necessary in some circumstances from both practical and regulatory standpoints. From the practical aspect of testing, it may not be possible to test the exact dosage form in an appropriate animal model. Thus, while the reinforcing capacity of nicotine may be established (Henningfield et al., 1985), the issue before FDA might be the abuse potential of a chewing gum containing nicotine. It is obviously not possible to determine the abuse potential of this dosage form in an animal model. The same type of issue arises in considering the problem of comparing an oral versus a smoked dosage form of a product or other dosage forms like sublingual or buccal delivery systems or transdermal patches. Similarly, dosage forms of abusable substances which are controlled release or delayed release dosage forms should be evaluated in human populations. From the regulatory viewpoint, it is often difficult to make the fine distinctions required for scheduling drugs under the CSA from animal data. Our advisory committees appear to prefer human data for regulatory decision making. Moreover, labeling claims from an industry sponsor, such as a low or insignificant abuse potential or lack of interaction with ethanol, will only be allowed if there is clinical evidence to support the claim.

Drug combinations are a special case from the regulatory standpoint. FDA recognizes that it is possible to add an ingredient to a dosage form to make it less abusable. This has been formalized in the codified policy stated in 21 CFR 300.50 (a)(2) which states that two or more drugs may be combined in a single dosage form when one component is added to minimize the potential for abuse of the principal ingredient. An example of this policy was the approval of pentazocine-naloxone combination in response to the T's and B's problem of the late 1970s and early 1980s (Senay 1985).

Combinations of psychoactive drugs are studied in both preclinical and clinical models. Although it is possible to determine whether a second

drug has an additive, potentiative, or antagonistic effect in preclinical modes, the clinical models offer additional information. Moreover, the controlled evaluation of combinations of drugs of abuse allows an evaluation of the basis of changing abuse patterns that are observed or reported. Thus, the study of an additive or "boosting" effect of a second drug on the "high" produced by the first drug can be determined in an appropriate population. For example, it was reported by several investigators that methadone maintenance patients were abusing benzodiazepines for the purpose of a heightened psychic effect (Woody et al., 1975; Kleber and Gold, 1978). Preston et al. (1984) examined the interaction of diazepam and methadone (150 percent of maintenance dose) and 40 mg of diazepam produced an increase in opioid subjective effects greater than that produced by either drug alone, Additionally, the subjects more frequently identified the combinations as benzodiazepine/ barbiturate-like. Thus, it is possible to validate a new abuse pattern in a study of the combination's effects on subjective states.

Drug combinations of an agonist and an antagonist also yield valuable information about the relative onsets, degree of blockade, and durations of action of such a combination. If an analgesic were being developed for marketing in combination with an antagonist, clinical studies in appropriate populations would be necessary to substantiate the effect of the antagonist on the combination with respect to both efficacy and abuse potential. Such an approach was used by Nutt and Jasinski (1974) in determining the effects of naloxoneonthe effects of orally and parenterally administered methadone.

Determination of subjective effects, changes in mood states, drug liking, drug preference, discriminative stimulus properties, and other psychopharmacological ratings serve as the first principle for comparison of the similarities and differences between a test drug and a standard. The primary analysis of the rating scales takes into account the dose-response characteristics of the test drug and the reliability of production of effects. In this manner, one can make inferences about the intrinsic efficacy of the drug (agonist, partial agonist, antagonist) and, in the case of opioid agonist/ antagonists, the relative efficacy of a drug for subreceptor types. Thus, drug effects which vary with the dose of drug administered (e.g., butorphanol (Jasinski et al., 1975, 1976) and nalbuphine (Jasinski and Mansky 1972)) can be determined through this type of clinical study. The time action curve for the production of subjective effects can also be determined from such studies.

Onset of subjective effects is another variable in the determination of abuse potential that appears to have face validity. Subjects consistently

prefer diazepam to oxazepam; the reason given is the more rapid onset of diazepam (Griffiths et al., 1984). Moreover, "pro-drugs," such as halazepam, also have a delayed onset (2-3 hours) and lower peak effects than diazepam (Jaffe et al., 1983).

A third principle in the clinical evaluation of abuse potential is the degree of overlap of the proposed therapeutic dose range and the doses which reliably produce subjective effects. An important consideration in the determination of abuse potential is what multiple of a standard therapeutic dose needs to be taken to reliably produce a desired state. Obviously, drugs which produce a desired state with a high degree of overlap of the therapeutic dose may have a high potential for abuse. Conversely, a drug which requires several multiples of the therapeutic dose to achieve a desired effect maybe considered less desirable, and therefore less abusable. This principle was employed in the decision to decontrol loperamide. It was shown that a 60 mg dose of loperamide (30 times the usual clinical dose) produced some noticeable drug effect in 44 percent of the subjects (Jaffe et al., 1980). Only one of nine subjects identified the drug as "dope."

Another major variable in the determination of abuse potential is the generalizability of "drug preference" in different subject populations. For example, in the determination of the abuse potential of diazepam, several investigators have carried out a series of studies to determine the degree of diazepam preference to placebo in volunteers (Johanson and Uhlenhuth 1980), young adults versus older adults (de Wit et al., 1985), anxious volunteers (de Wit et al., 1986), anxious patients being treated for anxiety (de Wit et al., 1987), and sedative-hypnotic abusers (Griffiths et al., 1980). The restriction of liking to populations with prior abuse histories suggests that the drug would have a more limited appeal than one that produced universal liking. It must be kept in mind, however, that this difference may be analogous to the differences in appeal between amphetamines and opiates. Thus, differences of this type are not a guarantee of a lack of abuse potential.

Other effects or consequences of drug intake that are amenable to study in human populations and can be related to both the therapeutic dose range and the dose range producing subjective effects include cognitive function, memory, presence or absence of hallucinations, psychomotor impairment, judgment about the level of intoxication or impairment, interactive effects with ethanol, and adverse effects such as behavioral disturbances and/or drug-induced psychiatric states; e.g., confusional states, drug-induced psychosis.

Two pharmacological properties of many drugs of abuse, that is tolerance and dependence, have not yet been addressed. The NDA regulations (21 CFR 314.50 (d)(5)(v)) state that an integrated summary of the studies demonstrating effectiveness should be written. The guidelines which accompany the regulations amplify on this section with respect to tolerance and dependence. The guidelines state that clinical studies of chronic drug effects should be analyzed for persistence of effectiveness, tolerance, and withdrawal effects. It is recognized that this approach may answer questions about the incidence of tolerance and physical dependence in the therapeutic dose range if the study has sufficient statistical power and the appropriate variables are being measured. Although studies of physical dependence in post-addict populations can theoretically still be carried out, I am unaware of any study of this type being performed since the Addiction Research Center left Lexington, Kentucky in 1976.

A field closely related to the assessment of abuse potential in human subjects is the development of agents to treat various types of drug dependence. In these types of studies, measures of physical dependence may be a primary variable. The efficacy and acceptability of induction regimens, dose ratios of the test and standard drugs, and patient acceptability can be studies in moderately small clinical trials. We have called these types of trials "pharmacological efficacy studies."

At this point, I would like to comment on an issue of internal state versus behavior as possible measures of drug efficacy in the treatment of drug dependence. Drug craving and drug seeking behavior are two other important components of the definition of psychological dependence. Although it is possible to construct scales which measure drug craving, changes in drug craving produced by an experimental agent are insufficient for the determination of the effectiveness to treat a drug dependence disorder. A reduction in craving must be accompanied by a reduction in illicit drug intake for the determination of efficacy. Operational variables such as reduced drug intake or cessation of intake are considered more persuasive than an effect on a more subjective variable such as craving. Moreover, the acceptance of a less than absolute reduction in drug intake as an acceptable efficacy variable may be limited to the opioids and alcohol dependence. For nicotine dependence, we have determined that a pharmacological agent should increase the quit rate.

Clinical studies of the abuse potential and dependence capacity of a new drug can be used for the following purposes: confirmation or negation of hypotheses developed from preclinical studies; determination of multiple psychopharmacological variables and their relationship to/overlap with the therapeutic dose range; determination of the onset, peak and duration

of effects in relation to the therapeutic dose range and the supra-therapeutic dose range; determination of changes in psychopharmacological effects as a function of dose, route of administration, and multiple doses (tolerance or accumulation); assessment of drug combinations for alterations in abuse potential; confirmation/refutation of purported claims in the product labeling; assessment of efficacy of treatment of physical dependence; assessment of statements in various sections of the product's labeling; and the necessity and propriety of scheduling under the CSA.

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CHAPTER 3

The Role of Abuse Liability Testing in Drug Control Procedures

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INTRODUCTION

The Comprehensive Drug Abuse Prevention and Control Act, commonly referred to as the Controlled Substances Act (CSA), was passed in 1970 to minimize the quantity of abusable substances available to those who are likely to abuse them and to provide for the legitimate medical, scientific and industrial needs for these substances in the United States. The Drug Enforcement Administration (DEA) is an agency within the Department of Justice and is primarily responsible for the administration and enforcement of the provisions of the CSA.

DEA had an operating budget of $490 million and a criminal investigative staff of 1,950 special agents in fiscal year (FY) 1987. DEA criminal investigations resulted in the arrest of more than 21,000 major drug violators and the conviction of more than 12,000 arrestees in FY 1987. During this time period DEA removed over 350 kilograms of heroin, 35,000 kilograms of cocaine, 632,000 kilograms of marijuana and more than 88 million dosage units of other controlled stimulants, depressants, hallucinogens and narcotics from the illicit market. DEA also seized 682 clandestine laboratories synthesizing controlled substances. Themajority of these laboratories were producing the central nervous system stimulants methamphetamine or amphetamine. Assets totalling over $500 million were also seized in FY 1987.

Both legitimately produced drugs and clandestinely manufactured substances were included in the original list of substances controlled under the CSA. Congress recognized that “Many of the drugs included (under the CSA)...have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people.” [21 U.S.C. 801(1)] Congress also found that, “The illegal

importation, manufacture, distribution and possession and improper use of controlled substances have a substantial and detrimental effect on the health and general welfare of the American people." [21 U.S.C. 801(2)] In consideration of the above, Congress made a determination that despite the legitimate medical need for certain substances, controls on their availability are necessary to protect the general health and well-being of the American people. For this reason a "closed system" of distribution was set up under the CSA for those who handle legitimately produced controlled substances. Such a system is aimed at reducing the diversion of legitimately produced pharmaceutical products into the illicit market and into the hands of drug abusers without disrupting the legitimate supply of controlled substances to those who have a bona fide need for them.

One of the key features of this closed distribution system is the registration by DEA of all manufacturers, distributors, practitioners and other persons who handle controlled substances in their legitimate businesses and professions (21 U.S.C. 822). Controls imposed by the CSA on DEA registrants include security standards (21 U.S.C. 821), production quotas (21 U.S.C. 826), order forms (21 U.S.C. 828), recordkeeping and reporting requirements (21 U.S.C. 827), prescription refill limits (21 U.S.C. 829), and import/export requirements (21 U.S.C. 952-959). Detailed regulations regarding these provisions of the law are found in Title 21 of the Code of Federal Regulations Part 1300 To End. The CSA provides civil, administrative and criminal penalties for those who fail to comply with these provisions of the CSA.

Currently there are more than 770,000 CSA registrants, the majority of whom (680,000) are practitioners, who are regulated by the diversion program at DEA. Investigations of registrants by DEA's 263 diversion investigators in FY 1987 resulted in more than 320 registrants surrendering their DEA registrations, the arrest of more than 75 major violators and the seizure of more than $2.2 million in assets.

DRUG CONTROL PROCEDURES

Both the criminal and regulatory provisions of the CSA apply only to specifically designated chemicals. When the CSA was passed in 1970 it included a list of controlled substances placed into one of five schedules based upon the abuse potential, accepted medical use and safety and physical and psychological dependence liabilities of each substance (21 U.S.C. 812). Regulatory controls and criminal penalties also vary according to these schedules. In passing the CSA, Congress realized that

new clinically useful drugs with abuse potential would be developed by the pharmaceutical industry and that enterprising clandestine laboratory operators would also synthesize noncontrolled substances with abuse potential solely for abuse purposes. A critical feature of the CSA is the authority granted to agencies of the executive branch of the Federal government to determine which substances should be controlled, rescheduled or removed from control. Several procedures for the control of substances which create or have the potential to create significant abuse problems have been established under the CSA and its amendments.

Traditional scheduling pursuant to 21 U.S.C. 811(a), (b) and (c) and 2 1 U.S.C. 812, emergency scheduling [21 U.S.C. 811(h)], the controlled substance analogue provision (21 U.S.C. 813), theschedulingofimmediate precursors [21 U.S.C. 811 (e)] and control actions required by international treaty obligations [21 U.S.C. 811(d)] are the specific procedures to administratively control or decontrol substances under the CSA. The term control also includes transferring substances between schedules [21 U.S.C. 802(5)].

The CSA provides roles for both the law enforcement and scientific and medical communities in making drug scheduling decisions pursuant to the traditional scheduling procedures. The Attorney General, who has delegated his authority under this statute to the Administrator of DEA, (28 CFR 0.100) and represents the law enforcement community, has the ultimate authority for the decision as to whether or not a drug should be controlled under this provision of the CSA and in which schedule. The DEA Administrator's decision, however, must be based on all available evidence and can be made only after a scientific and medical evaluation of that data is received by DEA from the Secretary of the Department of Health and Human Services (DHHS) (formerly the Department of Health, Education and Welfare), who is the Federal govemment's representative of the scientific and medical community. Recommendations of the Secretary of DHHS regarding scientific and medical aspects of scheduling are binding on DEA. If the Secretary of DHHS recommends that a substance not be controlled, the DEA Administrator may not control that substance [21 U.S.C. 811 (b)].

Traditional scheduling actions must involve "rulemaking proceedings on the record after opportunity for a hearing." Such rulemaking procedures under the CSA are governed by the Administrative Procedure Act (5 U.S.C.551-559). These procedures insure that interested and affected parties have an opportunity to express their views and to participate in the scheduling process by commenting on proposed scheduling actions or through participation in administrative hearings. Traditional scheduling actions are subject to judicial review by Federal appellate courts.

THE NEED FOR DATA

It is readily apparent that there is a critical need for scientifically sound, legally defensible and timely data relevant to each substance considered for placement into one of the five schedules of the CSA. None of the control mechanisms or criminal sanctions of the CSA are applicable to a substance unless that substance is properly scheduled under the CSA. Each of the procedures for controlling drugs requires gathering and evaluating relevant data before a scheduling decision can be made. Additionally, under each of the scheduling provisions of the CSA, DEA has the responsibility for defending the government's control actions in administrative hearings, Federal district and appellate courts and criminal proceedings. From the initial characterization of a newly encountered substance in forensic and preclinical pharmacology laboratories to questions about the relative physical dependence liability of an agonist-antagonist analgesic in humans to testimony at a criminal trial regarding whether an unstudied fentanyl analogue meets the criteria for a controlled substance analogue, DEA must rely on objective, accurate, scientifically derived and properly interpreted data.

Critical to the most efficient determination of whether a substance should be controlled or not and in which schedule is the timeliness of abuse and abuse liability data. This is particularly important for substances which have potential clinical utility and are in the marketing approval process. The Secretary of DHHS is required to submit information to DEA relevant to the scheduling of a substance if, at the time a new drug application (NDA) is submitted for a drug having a stimulant, depressant or hallucinogenic effect on the central nervous system, it appears that the substance has an abuse potential [21 U.S.C. 811(f)]. Scheduling determinations under the CSA for newly marketed substances without a history of actual abuse must be based on their abuse potential, their similarity to other substances and experiences with these substances in other countries if the substances are marketed there. The more data available and considered prior to the marketing of such drugs, the better the scheduling decisions. Decisions based on comprehensive data will ultimately be less costly to government, the affected industry and the public. Economic costs will be reduced but more importantly, the likelihood of individual or social injury, harm and criminal behavior will also be significantly decreased.

Inadequate data available when a drug is nearing the end of the marketing approval process makes it difficult for governmental authorities to make rational and timely scheduling decisions. These decisions can affect the

drug's availability as a legitimate medicine. The government can adopt a "wait and see" attitude toward the scheduling of the substance and allow it to be initially marketed in a noncontrolled status with subsequent review. This may result in unnecessary harm or injuries to individuals or the community if the substance is abused and produces deleterious effects. On the other hand, regulatory authoritiies can make a decision on whether to control a substance or not based on incomplete or equivocal data. Such decisions are more likely to be reversed after additional data is obtained or challenged in lengthy and costly administrative and legal proceedings. Such proceedings may delay the introduction of therapeutically useful drugs to the market or result in unnecessary harm to the public until the relevant data is developed or obtained. In extreme cases, the absence or incorrect interpretation of abuse and dependence liability data before a drug is introduced into the marketplace can ultimately result in the drug's removal from the market. Methaqualone is an example of such a worst case scenario.

METHAQUALONE CONTROL HISTORY

Methaqualone was initially marketed in the United States in 1965 as a noncontrolled sedative hypnotic amidst unsupported claims that it did not produce barbiturate-type physical dependence (Inaba et al., 1973; Anon. 1966). Medical use of methaqualone in the United States increased dramatically from 1968 totheearly 1970s (a 1500 percent increase between 1968 and 1973) when it was promoted as an effective daytime sedative and nighttime sleep aid without the disadvantages of the barbiturates (BNDD 1973).

Many of methaqualone's potentially harmful effects, including its abuse and dependence liabilities were however, reported in the literature outside the United States. In the 1960s methaqualone was introduced into the pharmaceutical market in many European and other countries and, in the decade following its introduction, methaqualoneachievedmuch notoriety as a drug of abuse (Falco 1976). Abuse of methaqualone in France, Italy, Sweden, Argentina, Norway, Ireland and Australia was reported during the 1960s (Falco 1976). Epidemic-like outbreaks of methaqualone abuse were also reported in Japan, Germany and Great Britain (Falco 1976; Madden 1966; Kato 1969; Ibe 1966).

In the United States, abuse of methaqualone was reported shortly after it wasfirstmarketed. Bytheearly 1970s methaqualone abuse was increasing in a manner and at a rate paralleling that of amphetamine in the 1960s (BNDD 1973). At the same time, reports of methaqualone's dependence

producing liability and the accompanying dangers of withdrawal were becoming more prevalent both in the United States and elsewhere (Falco 1976; Inaba et al., 1973). After gathering and reviewing the relevant data and after receiving a scheduling recommendation from the Secretary of DHHS, in a notice published in the Federal Register on April 6, 1973, DEA (at that time BNDD) proposed to place methaqualone into Schedule II of the CSA (38FR9170). Interestedpartiesrequested ahearingclaiming that while methaqualone had a high abuse potential, it did not produce severe physical or psychological dependence, a requirement for placing a substance into Schedule II of the CSA. A hearing was granted, evidence heard and a final decision was reached by the DEA Administrator to place methaqualone into Schedule II of the CSA effective October 4, 1973 (38 FR 27501).

Despite the tight controls of Schedule II, methaqualone diversion and abuse continued and increased. Several states (notably Georgia, Florida, New Jersey, Connecticut, Illinois, Mississippi, North Carolina and Texas) took additional actions to prevent the use (legitimate or other) of methaqualone (House Rpt. 1983). DEA lowered manufacturing quotas and increased enforcement activities regarding methaqualone but availability and abuse continued. Emergency room mentions reported by the Drug Abuse Warning Network (DAWN) increased 154 percent during the period 1978-1980 (Haislip 1983). Due to the widespread abuse of methaqualone and the public health risks associated with this abuse, Congress, in 1984, passed legislation (Public Law 98-329) whichordered DEA to transfer methaqualone from Schedule II to Schedule I of the CSA and ordered the Secretary of DHHS to withdraw marketing approval for methaqualone. These two actions were completed and methaqualone was removed from the market in the United States and placed into Schedule I of the CSA (49 FR 33870; 49 FR 36441). Methaqualone's widespread availability and abuse were not abated until it was removed from the market and placed into Schedule I of the CSA despite the most stringent controls of the CSA for marketed products. Had all the data regarding the hazards of methaqualone's use and abuse been acknowledged and properly evaluated prior to its introduction into the United States market and had it been scheduled accordingly at that time, early controls may have prevented the ensuing widespread availability, popularity and abuse which when uncurtailed led to the removal of this substance from the legitimate market.

EFFECTS OF CONTROL

The control status of a substance often effects how it is perceived by health care professionals as well as the general public. As evidenced by the methaqualone situation, perceptions of the abusability of a substance are slow to change if that substance is first marketed as an uncontrolled substance. Dextropropoxyphene, pentazocine and the benzodiazepines, diazepam and chlordiazepoxide are other substances which were first marketed as noncontrolled substances. Human experience with each of these drugs established that they had abuse and dependence liabilities warranting control under the CSA. Control of pentazocine, dextropropoxyphene, diazepam and chlordiazepoxide did not immediately alter the perception of the abuse and dependence potentials of these substances by physicians and patients.

No pharmaceutical firm wants to market a substance without assessing all potential forms of toxicity or adverse effects. Yet pharmaceutical firms may market new drugs without a resolution of their abuse potential or dependence-producing liability. Clearly, abuse potential and physical and psychological dependence liabilities are types of adverse effects which lead to behavioral and other toxicities. Some drugs, nonetheless may be promoted as safe, nonaddicting or less abusable alternatives to other controlled substances in similar therapeutic categories before conclusive scientific evidence is available to support such claims. Other abusable substances, such as MDMA, even though not marketed, are claimed to be safe, without a high potential for abuse and promoted for human use prior to the completion of even minimal preclinical studies (Greer 1983). Extensive efforts have been made to keep some of these substances uncontrolled. If appropriate testing, surveillance, evaluation and interpretation of data have been completed and such claims are warranted then no harm is done. On the other hand, however, if appropriate testing, surveillance, evaluation and interpretation are not done or if significant information is available but ignored, as in the cases of methaqualone and MDMA for example, the consequences can be serious.

Control actions (which include adding to, deleting from and transferring substances between schedules) under any of the provisions of the CSA must follow rigid administrative and legal procedures and be predicated upon scientifically valid and legally defensible data. The procedures and the nature and quantity of supporting data are dependent on the type of control action. In evaluating each substance for control under the CSA, DEA must keep in mind its mandate to limit the availability and supply of drugs to the illicit market without interrupting the supply of legitimate drugs to those who have a bona fide need for them. DEA must weigh the

ramifications of control of a substance on those who have a legitimate need for them against the need for restrictions on the availablity of a substance which causes harm to the public health and safety.

There are some who claim that national and international control (scheduling) of drugs has a negative impact on drug development and marketing and the use of pharmacologically active agents in the practice of medicine. There is no question that scheduling a substance under the CSA, or one of the international conventions, imposes additional requirements on those who handle these substances. DEA registration, quotas, recordkeeping, security, dispensing limitations, import/export requirements, etc., add varying levels of work and cost to manufacturers, distributors and dispensers of controlled substances. The economic burden is often passed to the consumer. For legitimate users of Schedule II through V controlled drugs, however, these burdens often are no more than minor inconveniences, particularly when compared to the benefits derived from them in the form of decreased public health and safety risks. For those who wish to work with Schedule I substances, especially if human studies are to be conducted, there are more stringent requirements (e.g., research protocol approval). In Grinspoon v. Drug Enforcement Administration, 828 F.2d 881(1st Cir. 1987), the Court of Appeals stated that, "From our review of the CSA, we can only conclude that Congress had already weighed the costs and benefits of legitimate research on dangerous drugs and has determined, in a categorical manner, that if the three Schedule I criteria are satisfied [see 21 U.S.C. 812 (b)(1)], then the substance should be subject to Schedule I controls even if this action will create administrative and other burdens for researchers." This statement by the Court of Appeals highlights the importance of obtaining and properly evaluating data regarding the three criteria for placing a substance into the appropriate schedule of the CSA. Despite the stringent controls of Schedule I, there have been several substances which have been moved from Schedule I into Schedule II when they were approved for marketing and the criteria for Schedule II were satisfied. Alfentanil, sufentanil and a dronabinol product (Marinol) are recent examples (52 FR 2516; 49 FR 22074; 51 FR 17476).

Scheduling, in general, has been successful in reducing the diversion of legitimately produced drugs to the illicit market (Jaffe 1985). One need only look at the decrease in the abuse problem involving legitimately produced amphetamines and barbiturates over the past years. Therapeutic agents are brought to the market based on a determination of their safety and efficacy by the Food and Drug Administration (FDA). If a product is therapeutically useful and particularly if it offers an advantage over other products indicated for the same medical condition, it will be utilized

whether or not it is scheduled. Codeine, the benzodiazepines, dextropropoxyphene, oxycodone and phenobarbital are among the most often prescribed drugs despite their abuse potential and control status under the CSA (Anon. 1987). In 1987 alone there were more than 85 million prescriptions written for the benzodiazepines. Drug scheduling also encourages the development of therapeutically useful substances without abuse or dependence-producing liabilities, a worthwhile goal regardless of CSA controls. The non-steroidal anti-inflammatory analgesics are recent examples.

The following description of the various scheduling provisions of the CSA attempts to delineate the kinds of data which are necessary and useful in determining whether or not a substance should be controlled under the CSA.

TRADITIONAL SCHEDULING

Traditional scheduling according to 21 U.S.C. 811(a-c) and 812 has been the procedure most commonly used by DEA to add, delete or transfer substances to, from or between the five schedules of the CSA. Unlike the emergency scheduling and controlled substance analogue provisions of the CSA, this procedure may be used for marketed as well as nonmarketed, investigational and clandestinely manufactured substances. Traditional scheduling must follow the Administrative Procedure Act regarding rulemaking proceedings, "on the record with an opportunity for hearing." This allows for interested parties to have their views considered either by comment or during an administrative hearing with judicial review available afterwards. Traditional scheduling involves the collection of all types of relevant data by DEA, a scientific and medical evaluation of that data by DHHS, an independent evaluation by DEA and specific findings by DEA regarding the relative abuse potential, accepted medical use and safety, and physical and psychological dependence potentials of the substance under review. Traditional scheduling actions may be initiated by DEA on its own, at the request of DHHS or at the request of any interested party. DEA most often initiates actions on clandestinely produced substances found in the illicit drug traffic. DHHS requests DEA to initiate scheduling actions for substances which are being introduced into the marketplace. Examples of other interested parties include pharmaceutical firms who want to change the scheduling status of one of their products or public interest groups. Traditional scheduling actions include the decontrol of substances, some of which were captured under the CSA because of their derivation from opium or opium alkaloids (e.g., naloxone and nalmefene)(39 FR 44392 and 36 FR 19116; 50 FR 45815). Other

non-opium derivatives (e.g., loperamide and dextrorphan) were decontrolled when data became available to show that these substances did not meet the criteria for control under the CSA (47 FR 49840; 41 FR 43401).

Both DEA and DHHS must consider the following eight factors listed in 21 U.S.C. 811(c) in making evaluations and scheduling recommendations for each substance under consideration:

(1) Its actual or relative potential for abuse.

The term potential for abuse, although not specifically defined in the CSA is found in the House Report 91-1444 and has the following meaning when applied to a substance with a stimulant or depressant effect on the central nervous system or hallucinogenic effect:

(a) Evidence that individuals are taking it in amounts sufficient to create a hazard to their health or to the safety of other individuals or the community; OR
(b) Significant diversion from legitimate channels; OR
(c) Individuals are taking it on their own initiative rather than on the medical advice of a licensed practitioner or other qualified health professional; OR
(d) The drug is so related in its action to a drug already listed as having a potential for abuse to make it likely that the drug will have the same potential for abuse, thus making it reasonable to assume that (a), (b), and/or (c) above will occur (House Rpt. 1970).

Data regarding actual abuse, clandestine manufacture, trafficking and diversion from legitimate channels as well as preclinical and clinical abuse liability studies are considered under this factor. Specific information, animal or human, whether from controlled experiments or general human experience, which could be used to determine or predict the abuse potential of a substance is evaluated by DEA and DHHS. It is important to note that this factor includes the modifier "relative" when describing abuse potential. This means that the abuse potential of a new substance should be compared to that of a substance with a known abuse potential. Comparisons are usually made to prototypic drugs such as morphine (narcotic), LSD (hallucinogen), dextroamphetamine (stimulant) or one of the barbiturates (depressant). It is essential, therefore, that abuse liability studies contain a quantitative as well as a qualitative component. The specific findings required by 21 U.S.C. 812 and necessary to schedule a substance under the CSA also require a determination of relative abuse potential.

Thus it is important to characterize a substance not only as having an abuse potential but also whether its abuse potential is high, moderate or low relative to substances with known high, moderate or low abuse potentials. Determinations of this sort are complicated by such testing variables as dose, route of administration, acute or chronic use, species and set and setting, but nonetheless are necessary. Further, if a substance behaves somewhat differently than a prototypic drug in animal tests this may not mean that it does not have an equivalent or otherwise significant abuse potential. For example, 3,4-methylenedioxyamphetamine (MDA), a Schedule I substance with a known high abuse potential, is recognized as bothd-amphetamine-like and DOM-like by rats trained to discriminate these drugs from saline (Glennon and Young 1984). The drug, 3,4-Methylenedioxymethamphetamine (MDMA), also in Schedule I and having a high abuse potential, is recognized only as d-amphetamine-like in the same tests (Glennon and Young 1984; Glennon et al, 1982). The drug, 3,4-Methylenedioxy-N-ethylamphetamine (MDE; EVE) and 3,4-methylenedioxy-N-hydroxyamphetamine (N-hydroxy-MDA) in rodent drug discrimination studies with *d*-amphetamine and DOM as training drugs, do not generalize to either *d*-amphetamine or DOM (Glennon et al., 1988). Based on this information alone it would appear that MDE and N-hydroxy-MDA are neither amphetamine-like stimulants nor DOM-like hallucinogens. These studies alone would further suggest that MDA, MDMA, MDE and N-hydroxy-MDA have different abuse potentials.

However, further studies with MDMA as the training drug, show that both MDE and N-hydroxy-MDA produce MDMA appropriate responding (Glennon 1988). Additionally, the substances tested thus far (MDA, MDMA and MDE) are self-administered by primates trained to self-administer cocaine (Griffiths et al., 1976, 1988; Lamb and Griffiths 1987; Beardsley et al., 1986). It has also been reported that in humans, MDA, MDMA, MDE and N-hydroxy-MDA exhibit a similar psychopharmacological profile (Braun et al., 1980). Further all four substances are clandestinely produced, distributed and abused in significant quantities. It appears from these and other data that all four substances have equivalent potentials for abuse.

(2) Scientific evidence of its pharmacological effects.

The best available knowledge of the pharmacology of the substance is considered under this factor. The CSA classifies controlled substances as stimulants, depressants, hallucinogens and narcotics. The pharmacology of each substance is examined to determine whether it fits one or more of the above pharmacological categories. The more points of comparison between the subject drug and prototypic comparison drugs that are available the better.

(3) The state of current scientific knowledge regarding the substance.

Scientific data other than the pharmacology of a substance are considered under this factor. Chemical and physical properties of a substance which may influence whether or not or to what degree a substance may be abused are examined. Thesyntheticpathway, including ease of synthesis, availability of precursors, yield and expected impurities, solubility, salt forms, isomers and medical and other uses are examples of the types of information examined. The chemical and physical properties and the likelihood of clandestine synthesis affect the determination of a substance's abuse potential. If a substance is not water soluble, it is not likely to be injected; if the synthesis of a substance requires hard to find precursors, elaborate equipment or complex techniques, it is less likely to be clandestinely synthesized.

(4) Its history and current pattern of abuse.

It is important to know how a substance is abused, under what circumstances, and the social, economic, and demographic characteristics of the population abusing the substance. The history of the substance's legitimate use and abuse should also be considered. DEA must also assess the social significance and economic impact of any control actions.

(5) The scope, duration and significance of abuse.

Whether abuse of a substance is an isolated instance in one location or a widespread recurring phenomenon is necessary information when trying to determine whether or not a substance should be controlled under the CSA. The problem, or potential problem, with a substance must be large or pervasive enough for DEA to determine that Federal control under the CSA is warranted. All states have controlled substances laws, most of which are patterned after the Federal CSA. States may schedule substances in response to Federal scheduling or independent of DEA actions. DEA must determine if control measures taken at the state level are sufficient or if Federal intervention is warranted. DEA is not required to wait until an abuse problem reaches large proportions or is prevalent across the country (House Rpt. 1970). The significance of the abuse of a new substance in a few areas may be indicative of future widespread abuse; DEA must make this evaluation based on available data. The seriousness and potential spread of the clandestine synthesis, distribution and abuse of fentanyl and meperidine analogues, potent narcotic substances, were sufficient to prompt DEA to control them under the CSA even though they had been identified in only a few areas.

There have been suggestions that the control status of glutethimide be evaluated by DEA. Glutethimide is currently in Schedule III of the CSA and is abused in combination with codeine ("Loads," "Fours and Dors") by significant populations in certain areas. A number of states with problems have already placed glutethimide into Schedule II. DEA must determine whether the state response is adequate or whether the problem is widespread and significant enough for the Federal government to initiate action. Reliable data, particularly from human experiences with glutethimide, is critical to a wise scheduling decision.

(6) What, if any, risk there is to the public health.

The risk to the public health by a substance may manifest itself in many ways. Abuse of drugs may affect the physical or psychological functioning of the individual abuser; it may have disrupting effects on the abuser's family, friends and society in general. Abuse of certain drugs leads to violent behavior, endangering others; abuse may be associated with criminal activities; the effects of some drugs on psychomotor functioning, and thus on driving, have been well documented.

Data examined under this factor range from preclinical toxicity test results to postmarketing adverse reaction data in humans. DEA reviews data from crime laboratory chemists, forensic toxicologists, medical examiners, poison control centers, medical emergency rooms, drug treatment centers, and the scientific and medical literature. It is important that adverse health effects be reported either in the published literature or directly to the responsible government agencies (FDA, DEA and NIDA) so that this data is available when scheduling decisions are being made.

(7) Its psychic or physiological dependence liability.

The ability of a substance to produce physical or psychological dependence in users is one of the more important factors for DEA (and DHHS) to address in determining whether or not a substance should be scheduled under the CSA. This is particularly true for substances which either are marketed or are being investigated for marketing. In order for a substance to be placed into Schedules II through V, it must be determined that the substance is capable of producing a degree of physical or psychological dependence. Physical or psychological dependence liability is one of the three specific criteria which must be satisfied for a substance to be placed into Schedules II through V. As evidenced by the history of methaqualone scheduling and supported by similar experiences (with the benzodiazepines, some agonist-antagonist analgesics and other substances),

it is this finding which is the most difficult to establish and is often challenged. This specific finding is not necessary for contolling substances without accepted medical use in Schedule I but it is a factor that nonetheless, must be considered.

Others will address the specific means for determining the physical and psychological dependence liability of substances. The essential point, however, is that not only must appropriate preclinical or clinical testing and/or postmarketing surveillance be conducted but that the observations of these studies and experiences must be evaluated carefully and objectively.

(8) Whether the substance is an immediate precursor of a substance already controlled.

The CSA provides for the control of immediate precursors of controlled substances in the same or higher numbered schedule as the controlled substance of which it is an immediate precursor [21 U.S.C. 811(e)]. The term "immediate precursor" is defined in the CSA [21 U.S.C. 802(22)] to mean a substance:

(A) which the Attorney General has found to be and by regulation designated as being the principal compound used, or produced primarily for use, in the manufacture of a controlled substance;
(B) which is an immediate chemical intermediary **used** or likely to be used in the manufacture of such controlled substance; and
(C) the control of which is necessary to prevent, curtail, or limit the manufacture of such controlled substance.

Administrative control of immediate precursors may proceed without regard to the procedural requirements of 21 U.S.C. 811(a) and (b) and without the involvement of DHHS. The control of precursors of immediate precursors is prohibited by the CSA [21 U.S.C. 811(e)]. Substances administratively controlled specifically because they are immediate precursors include the phencyclidine precursors, 1-piperidinocyclohexanecarbonitrile (PCC) and 1-phenylcyclohexylamine (43 FR 21324) and the amphetamine/methamphetamine precursor phenytacetone (P-2-P) (44 FR 71822).

Once these eight factors are evaluated by DHHS and DEA and a scheduling recommendation is received from the Secretary of DHHS, the DEA Administrator determines whether the available data regarding the

substance under review can support the findings required by 21 U.S.C. 812 for any of the five schedules. The findings required by 21 U.S.C. 812(a) are as follows:

(1) Schedule I.
(A) The drug or other substance has a high potential for abuse.
(B) The drug or other substance has no currently accepted medical use in treatment in the United States.
(C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.

(2) Schedule II.
(A) The drug or other substance has a high potential for abuse.
(B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
(C) Abuse of the drug or other substance may lead to severe psychological or physical dependence.

(3) Schedule III.
(A The drug or other substance has a potential for abuse less than the drugs or other substances in Schedules I and Il.
(B) The drug or other substance has a currently accepted medical use in treatment in the United States.
(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

(4) Schedule IV.
(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.
(B) The drug or other substance has a currently accepted medical use in treatment in the United States.
(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

(5) Schedule V.
(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.
(B) The drug or other substance has a currently accepted medical use in treatment in the United States.
(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

If the available data regarding the substance under review does not support the required findings for control in one of the five schedules of the CSA, that substance is not controlled at that time. The substance may remain

under scheduling review pending receipt of more data and a new evaluation by DEA and DHHS may occur at a later date. If the DEA Administrator determines that a substance meets the criteria for control in one of the five schedules under the CSA or that it should be decontrolled or transferred into another schedule, a proposal to do so is published in the Federal Register. Opportunities for comments or hearings are provided. If there are no hearing requests a final order is published in the Federal Register and the control action becomes final. Relevant comments must be considered by DEA and addressed in the final order. If there is a request for a hearing on relevant matters, one is held before an Administrative Law Judge (ALJ) who makes recommendations to the DEA Administrator. The Administrator then considers the entire record, including the recommendations of the ALJ, and publishes his decision as a final rule in the Federal Register. The DEA Administrator is not required to follow the recommendations of the ALJ. The decision of the Administrator can be reviewed by appellate courts at the request of interested parties. The recent cases of buprenorphine and MDMA are examples of the entire scheduling process from initial proposal to place the substances under the CSA through administrative hearings and appellate review. Buprenorphine was proposed for control in Schedule V of the CSA on September 20, 1982 and the effective date of final control was February 28, 1985 (50 FR 8 104). MDMA was proposed for Schedule I control on July 27, 1984 and the effective date of final control was March 23.1988 (53 FR 5156). In both cases the process took several years to complete.

EMERGENCY SCHEDULING

The comprehensive Crime Control Act of 1984 (Public Law 98-473) which became effective on October 12, 1984, amended the CSA to provide DEA with emergency scheduling authority [21 U.S.C. 811(h)]. Specifically DEA has been given authority to place a substance into Schedule I of the CSA for a period of one year (with a possible six month extension) in certain situations without going through the traditional scheduling procedure outlined above. A substance may be temporarily controlled only if the DEA Administrator finds that such scheduling is necessary to avoid an imminent hazard to the public safety. The emergency scheduling provision may only be applied to substances which are not approved for marketing or are exempted for investigational use by FDA under the Federal Food, Drug and Cosmetic Act [21 U.S.C. 811(h)]. The Secretary of DHHS, although not required to evaluate substances considered for emergency control by DEA, must be notified of DEA's intention to invoke its emergency scheduling authority, and DEA must

take into consideration any comments by the Secretary, particularly those relating to the marketing status of the substances. The emergency scheduling authority was given to DEA in an effort to streamline the scheduling process in response to the growing problem of controlled substance analogues ("designer drugs").

DEA is required to consider three of the eight factors in 21 U.S.C. 811 (c) in making a determination as to whether a substance should be temporarily placed into Schedule I of the CSA pursuant to the emergency scheduling provisions. These factors are (1) the history and current pattern of abuse, (2) the scope, duration and significance of abuse, and (3) the risk to the public health. DEA has used its emergency scheduling authority on six occasions since April 1985 to temporarily place 16 substances into Schedule I. There were ten analogues of the potent narcotic analgesic fentanyl: (1) 3-methylfentanyl (N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]-N-phenylpropanamide), (2) acetyl-alpha-methylfentanyl (N-[1-(1-methyl-2-phenylethyl)-4-piperidyl]-N-phenylacetamide), (3) beta-hydroxyfentanyl (N-[1-(2-hydroxy-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide), (4) beta-hydroxy-3-methylfentanyl (N-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N-phenylpropanamide), (5) para-fluorofentanyl (N-(4-fluorophenyl)-N-[1-(2-phenylethyl)-4-piperidyl]propanamide), (6) thiofentanyl (N-phenyl-N-[1-(2-thienyl) ethyl-4-piperidinyl]-propanamide), (7) 3-methylthiofentanyl (N-[(3-methyl-1-(2-phenyl) ethyl-4-piperidyl]-N-phenylpropanamide), (8) alpha-methylthiofentanyl (N-[1-methyl-2-(2-phenyl) ethyl-4-piperidyl]-N-phenylpropanamide), (9) benzylfentanyl (N-[1-benzyl-4-piperidyl]-N-phenylpropanamide) and (10) thenylfentanyl (N-[1-(2-thenyl)methyl-4-piperidyl]-N-phenylpropanamide); two analogues of the narcotic analgesic meperidine: (1) MPPP (1-methyl-4-phenyl-4-propionoxypiperidine) and (2) PEPAP (1-(2-phenethyl)-4-phenyl-4-acetoxypiperidine); three analogues of the hallucinogenic amphetamine MDA: (1) MDMA (3,4-methylenedioxy-N-methylamphetamine), (2) MDE (3,4-methylenedioxy-N-ethylamphetamine) and (3) N-hydroxy-MDA (3,4-methylenedioxy-N-hydroxyamphetamine); and 4-methylaminorex (2-amino-4-methyl-5-phenyl-2-oxazoline), an amphetamine-like substance. These substances were emergency scheduled based on their appearance in the illicit market, their similarity in chemical structure to that of controlled substances and the likelihood that they would produce pharmacological effects similar to those of prototypic Schedule I or II substances. Often there is no biological data available prior to the emergency control of illicitly produced and abused substances. Therefore, information derived from structure-activity relationship considerations plays an important role in emergency scheduling.

In order to keep an emergency scheduled substance in Schedule I, DEA must initiate traditional scheduling procedures for that substance during the one year period in which it is emergency controlled and complete the action before the expiration of 18 months. The time limitations of emergency scheduling underscore the need for timely abuse liability data and the need to determine the most efficient tests to provide the data necessary to make permanent scheduling decisions. During the one year temporary scheduling period, DEA must acquire sufficient data to make a determination as to whether or not the emergency scheduled substance should remain under the CSA. Often the substances have never been studied nor are they available for study. DEA, as soon as possible after identifying a newly abused substance, provides for the synthesis of this substance for analytical reference standards and biological testing. Only then can the appropriate pharmacological and abuse liability tests be conducted. Thus far two of the substances which were temporarily controlled (benzylfentanyl and thenylfentanyl) were not permanently controlled when studies did not provide evidence that they had an abuse potential. Both of these substances were found in street samples with other fentanyl analogues and were most likely unreacted intermediates in the synthesis of the target fentanyl analogues. Eleven of the temporarily controlled substances are now permanently controlled; three substances have been proposed for permanent control and one was emergency scheduled only recently.

CONTROLLED SUBSTANCE ANALOGUES

Despite the emergency scheduling authority granted to DEA, clandestine laboratory operators continued to synthesize new analogues of controlled substances faster than DEA could schedule them. The CSA was again amended in October 1986 by enactment of the Controlled Substance Analogue Enforcement Act as part of the Anti-Drug Abuse Act of 1986. This law provides for controlled substance analogues to be treated as Schedule I substances to the extent that they are intended for human consumption (21 U.S.C. 813). A controlled substance analogue is defined as a substance which (1) has a chemical structure substantially similar to that of a controlled substance in Schedules I or II; (2) has a stimulant, depressant or hallucinogenic effect on the central nervous system that is substantially similar to or greater than that of a controlled substance in Schedules I or II; or (3) a particular person represents or intends to have a stimulant, depressant or hallucinogenic effect substantially similar to or greater than that of a controlled substance in Schedules I or II [21 U.S.C. 802(32)]. The term controlled substance analogue does not include controlled substances, drugs with approved new drug applications or

with respect to a particular person, any substance for which an exemption is in effect for investigational use, for that person, under section 505 of the Federal Food, Drug and Cosmetic Act.

This amendment to the CSA provides a means to prosecute those who attempt to circumvent existing drug laws by manufacturing anddistributing substances with chemical structures which are only slightly different from those of controlled substances and which are likely to retain the psychoactive properties of the parent compounds. There is no list of controlled substance analogues. Expert testimony may be heard in each criminal trial to determine if a substance meets the criteria for a controlled substance analogue. Structure-activity relationships, although no substitute for actual biological data, form an important element in determining whether or not a substance is a controlled substance analogue. Points of pharmacological similarity or dissimilarity are used whenever they are available. If the same controlled substance analogue is encountered in the illicit drug traffic with some frequency, DEA may initiate the emergency or traditional scheduling provisions of the CSA, dependent upon the type and quantity of available data. To date this provision of the CSA has been successfully used on several occasions to convict individuals who have manufactured or distributed analogues of controlled substances.

Unlike traditional scheduling which provides for an administrative hearing procedure and judicial review prior to the inclusion of a substance under the CSA, whether or not a substance is a controlled substance analogue under the CSA is often challenged in criminal trials. Once a substance is scheduled under the CSA there is little debate as to whether that substance is classified as a controlled substance. Individuals who are prosecuted for the manufacture or distribution of a controlled substance analogue can force the prosecution to prove on each occasion to a judge and/or jury that a substance meets the criteria for inclusion under the term controlled substance analogue. The responsibility falls on DEA to advise attorneys whether or not a particular substance falls within the definition of a controlled substance analogue. Subsequently DEA staff or others may provide expert testimony regarding these matters.

INTERNATIONAL TREATY OBLIGATIONS

The United States is a party to two international drug control treaties, the Single Convention on Narcotic Drugs, 1961 and the Convention on Psychotropic Substances, 1971. The Single Convention is responsible for the international control of narcotics which, by definition, includes marijuana and cocaine. The Psychotropic Convention is responsible for

the international control of stimulants, depressants and hallucinogens. The CSA requires that DEA must control narcotic substances scheduled under the Single Convention in the most appropriate CSA schedule to carry out the obligations of the United States under the treaty. Scheduling under these circumstances is done without regard to the findings and procedures required for traditional scheduling[21 U.S.C. 811 (d)(1)]. If a substance is internationally controlled under the Psychotropic Convention, the CSA provides an elaborate set of procedures in accordance with the traditional scheduling process to control that substance under the CSA [21 U.S.C. 811 (d)(2)-(5)].

Prior to the review of substances by the World Health Organization for possible international control, DEA, along with other Federal agencies, industry groups and others, provide whatever data are available regarding the abuse, abuse potential, trafficking and diversion of the substances to be reviewed.

CONCLUSION

Human abuse liability testing is one of the means available to scientists to attempt to assess the likelihood that a psychoactive drug will be abused. Results of abuse liability studies coupled with other pharmacological tests and evidence of actual abuse, clandestine manufacture, distribution and diversion of a psychoactive substance provide DEA and DHHS with the information necessary to make informed scheduling decisions under the CSA. DEA urges that some form of abuse liability testing become part of the standard premarketing testing performed on drugsacting on the central nervous system. Such testing should be conducted as soon as practical in the drug development process and the results made available to the appropriate regulatory authorities. Further, DEA urges that existing abuse or abuse liability data from other countries or data on related substances be made available and considered prior to the marketing of new drug products. Only if scientifically valid and legally defensible data is generated, made available, considered and objectively evaluated in a timely manner, can the most effective measures be taken to ensure that the general health and welfare of the American public is protected. Such scheduling decisions will enable DEA to limit the availability of new abusable substances to those likely to abuse them while providing for the legitimate need for these substances in the United States.

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CHAPTER 4

Historical Perspectives on the Use of Subjective Effects Measures in Assessing the Abuse Potential of Drugs

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INTRODUCTION

This overview of the history of the use of subjective effects measures in the assessment of abuse potential of drugs will touch upon two related themes: 1) subjective responses to psychoactive drugs and the idea that responses are linked to the likelihood of nonmedical drug use; and 2) systematic measurement of subjective responses to drugs and the prediction of the likelihood that a drug will be abused within the current legal meaning of the term. We would like, at the outset, to acknowledge our debt to several major sources. These include Terry and Pellens (1928), Corti (1932), Beecher (1959), Holmstedt and Liljestrand (1963), Lewin (1964), Holmstedt (1967), Caldwell (1970), Eddy (1973), Musto (1973), Brecher (1972), Byck (1974), Jasinski (1977), Berridge and Edwards (1981), Kramer (1980, 1981), and Siegel (1984). Hardly more than a sampling, these sources provide fascinating historical, anecdotal, and scientific reading relevant to the topic of this conference.

EARLY DESCRIPTIONS OF SUBJECTIVE EFFECTS OF SOME WELL KNOWN DRUGS OF ABUSE

Descriptions of the subjective effects of many naturally occurring drugs can be found in the earliest writings of civilization. The acute subjective effects of wine and the effects of chronic intoxication are well described in the Old Testament. Both the Greek and Roman pantheons had gods of wine and drinking, and the literature of both cultures contains detailed descriptions of drunkenness. Homer (circa 500 B.C.E.) tells us, in The Odvssev, of the wonderful effects of the drug, nepenthes, that Helen mixed with the wine of her guests so that they might feel less saddened

by the absence of Ulysses and the loss of loved ones. Although other translators have been less specific for our purposes, Fitzgerald uses these words:

> But now it entered Helen's mind
> to drop into the wine that they were drinking
> an anodyne, mild magic of forgetfulness.
> Whoever drank this mixture in the wine bowl
> would be incapable of tears that day-
> though he should lose mother and father both,
> The opiate of Zeus's daughter bore this canny power.
> *Homer, The Odyssey IV, 219-228.*

Lewin (1964), the noted psychopharmacologist, concluded that nepenthes could be no drug other than opium, but Moreau (1845, translation, 1973) appears to accept the view that nepenthes was Cannabis Indica. Whatever the drug, Homer expressed little concern that nepenthes would come to be used on a regular basis.

The Greek historian, Herodotus (486-406 B.C.E.), may have been the first observer to describe for us the effects of hemp (cannabis), when he reported that the Scythians threw hemp seeds on hot rocks, inhaled the vapors, then danced, sang, and generally seemed quite joyous. However, Herodotus made no comment on the possibility of abuse or misuse.

Although the definition of drug abuse has varied greatly over the years and across cultures, concern that the subjective effects of a drug would lead to misuse are not of recent origin.

Alcohol

For much of recorded history, only in the case of alcohol was there a clear recognition that drug use could lead to excessive drug use. Descriptions of the effects of alcohol, as well as admonitions to use the drug in moderation are found throughout the non-medical literature, from the Bible through Shakespeare, as well as in the writings of 17th, 18th, and 19th century men of medicine.

Writing in the early 1800s, Benjamin Rush expressed the belief that "ardent" (distilled) spirits were frequently associated with drunkenness. He advised against their use (although he saw no harm in naturally fermented drinks). Rush also provided a lively description of the subjective

and behavioral effects of ardent spirits during intoxication, but it is not clear that he ever carried out a study of alcohol.

Tobacco

One of the earliest written descriptions of the effects of tobacco smoking was provided by Bartolomeode las Casas, who accompanied the Spanish explorers to the New World in the early 1500s. Interestingly, this is one of the few instances in which a description of subjective effects and concerns about repetitive use and inability to cease drug use are provided by the same observer:

> The herb which the Indians inhale is rolled up like a sort of bundle in a dried leaf . . . They then light one end of it and draw in the smoke at the other; the effect is a certain drowsiness of the whole body accompanied by a species of intoxication, in which state they declare that they no longer feel any sense of fatigue. The . . . tobaccos, as they call them, have been adopted also by the settlers in this region; I have seen many Spaniards in the island of Hispaniola who used them and who, when reproached for such a disgusting habit, replied that they found it impossible to give it up.
> *Corti 1932, p. 32.*

When tobacco was first introduced into Europe, its use engendered considerable resistance and, in some cases, extreme sanctions. Almost from the start, critics linked its subjective effects to its capacity to produce addiction - an irresistable urge to continue to use it. One such critic was James I of England who, in 1604, wrote with scathing scepticism about the reported useful effects of tobacco:

> . . . what greater absurdities can there bee, than to say that one cure shall serve for divers, nay, contrarious sortes of diseases? . . . It helpes all sorts of Agues. It makes a man sober that was drunke. It refreshes a weary man, and yet makes a man hungry. Being taken when they goe to bed, it makes one sleepe soundly, and yet being taken when a man is sleepie and drowsie, it will, as they say, awake his braine, and quicken his understanding . . . many in this kingdome have had such a continuall use of taking this unsavorie smoke, as now they are not able to forbeare the same, no more than an olde drunkard can abide to be long sober, without falling into an

> uncurable weaknesse and evill constitution . . . to take a custome in anything that cannot be left againe, is most harmfull to the people of any land.
> *Corti 1932, pp. 79-80.*

Opium

While recognition of opioid dependence probably came after recognition of dependence on alcohol and tobacco, its remarkable persistence has given it a special place among the addictions. It may also have so special a place because the withdrawal syndrome associated with cessation is dramatic, distressing and so reproducible that, once pointed out, its relation to drug use and cessation has rarely been questioned.

In 1700, an English pharmacist, John Jones, published The Mysteries of Opium Reveal'd. Although he recognized the danger of "long and lavish use," and of discontinuation after such excess, his treatise was largely laudatory. He believed that most of the problems encountered with opium were due to impurities. John Jones is frequently given credit for linking the persistence of opium use to the withdrawal syndrome that follows cessation, a link that is rarely questioned. He proposed a method of gradual dose reduction to ease the severity of withdrawal (Kramer 1980, 1981). In a dubious tribute to his early insight, opiate addicts continued to describe the severity of their habit as the size of their "Jones" well past the middle of the 20th century.

During the next several decades, the use of opium was widely recommended and used for diverse disorders. During these years its capacity to alter mood and elevate the spirits became generally well known. However, according to Kramer (1981), at least one observer expressed considerable concern. In 1763, John Awsiter, apothecary to Greenwich Hospital wrote An Essay on the Effects of Opium Considered as a Poison. In it he expressed the concern that if the pleasure-giving properties of the drug were to become well known, there would be widespread habituation, which would be a general misfortune.

Thus by the mid-18th century, two views of opium addiction had been put forth: people continue to use the drug because of the distress of withdrawal, or people use it repeatedly to experience its pleasure-giving effects.

By the turn of the 19th century, direct experimentation had begun to replace clinical observation. Weber, experimenting on himself, may have been among the first to describe the subjective effects of opium. Seturner,

best known for his isolation of morphine from opium in 1805, was also the first to describe the subjective effects of morphine which he administered to himself and his students (Kramer 1980).

Inhalants

Another milestone in the history of studying the subjective effects of drugs is the work of Humphrey Davy. In 1800, Davy wrote a 600 page book in which he provided detailed descriptions of the effects of nitrous oxide, which he took himself and administered to friends, students and colleagues. The poet, Robert Southey said, after one of Davy's nitrous oxide parties, that the highest possible heaven must have an atmosphere of nitrous oxide (Brecher 1972). If it occurred to Davy that some day in the future, some people would be concerned about the misuse of nitrous oxide or other inhalants, he did not emphasize the point.

Cannabis

J.-J. Moreau de Tours (1845) carried out extensive research on hashish. He took it himself and he subsequently recruited his students as subjects, but generally he had more success in recruiting his artistic friends than his scientific associates. Holmstedt (1967) writes that Moreau's methodology was meticulous and that he is justly viewed as the grandfather of psychopharmacology. Although he did not employ placebos or double-blind methodology, he did use a range of dosages and his descriptions of the effects of hashish, and particularly of its euphoric effects, are still worth reading today. He also experimented with opium andthebelladonna alkaloids, using similar methodology and subject material. In his writing he reviews the literature on the effects of other psychoactive drugs, quoting extensively from Davy's work on nitrous oxide. Moreau was familiar with general concepts of alcohol and opium dependence, and was also aware that addiction to hashish was common among the Moslems, and that some chronic users developed a state of chronic apathy. Nevertheless, he believed that cannabis might have important therapeutic actions.

He compared the risk of hashish dependence to the risk of alcoholism and believed that in both cases the risks did not argue for prohibiting the proper utilization of the substances (Moreau, translation 1973).

Cocaine

Freud's review of cocaine in 1884, Uber Coca, is by any criterion a landmark in the history of measuring the subjective effects of drugs and

attempting to predict their abuse potential. In the tradition of Davy, Seturner, and Moreau, Freud carried out experiments on himself, friends, and colleagues. He reported that cocaine produces an "exhiliration and lasting euphoria, which does not differ in any way from the normal euphoria of a healthy person." He also described its effects on fatigue, hunger, and need for sleep. Freud was well aware of the notion of drug dependence, but expressed the view that, used in moderation, even over long periods, cocaine would not have detrimental effects on the body. Freud speculated that the drug might have uses in the treatment of melancholia, and citing American work as a precedent, he advocated the use of cocaine in the treatment of morphine addicts. He considered, but minimized, the possibility that such treatment would merely substitute one addiction for another, expressing the view that cocaine use would be only temporary (see Byck 1974).

Reaction to Freud's paper came rapidly. In a review published in 1885, Louis Lewin, the great toxicologist, stated that cocaine was contraindicated in morphine withdrawal. He emphasized that it is the distinct variety of euphoria produced by opiates which the opiate user seeks and that administering cocaine simply produces a double addiction, similar to what is seen when opiate users drink chloroform or ether (see Caldwell 1970). This was followed in 1888, by Erlenmeyer's scathing rebuttal to Freud's advocacy of cocaine, in which he reported 13 cases of iatrogenic cocaine addiction in morphine addicts (Berridge and Edwards 1981).

Hallucinogens

No survey of research on subjective effects of drugs could omit some mention of the work of Emil Kraepelin, or Louis Lewin or Arthur Heffter. Kraepelin's systematic investigations included work on the psychic effects of morphine, alcohol, paraldehyde, ether, amyl nitrite, as well as other drugs. Holmstedt and Liljestrand (1963) credit Kraepelin with publishing, in 1892, the first scholarly account of the effects of drugs on mental function.

Lewin carried out studies in a number of areas, including chronic morphinism, in the 1870s. Both Lewin and Heffter independently studied the subjective effects of mescaline in the 1890s.

Hefftercarriedout heroic studies using himself as a subject. He is described as a stolid, somewhat boring lecturer. It is not too surprising that he experienced little of the mystery that others have described in connection

with these agents. His view of abuse potential of hallucinogens is summed as follows:

> ...Weir Mitchell and Ellis believe that peyote (mescal) will also become popular amongst cultured people as an intoxicating drug. I think that this is unlikely because the results which I obtained on myself show that the side-effects are so pronounced that they considerably spoil the appreciation of the beautiful visual images.
> *Holmstedt and Liljestrand, 1963.*

Amphetamines

Until about 1932, when amphetamine (synthesizedin 1877) was introduced into medicine as a drug for treatment of nasal congestion, cocaine occupied a unique place as an abusable stimulant. By 1935, the utility of amphetamines in narcolepsy, as well as some of its CNS stimulant effects, had been recognized. By the early 1940s, its euphorigenic and mood altering effects were also well recognized. Nathanson (1937) carried out a study of amphetamine remarkable for its sophistication. It involved 40 outpatients who were "suffering" from nervous exhaustion and 55 young normal individuals who were given 20 mg of amphetamine and 25 comparable normals who were given placebo. The study involved the use of self-rating questionnaires. The most frequent effect in normal subjects wasasenseof well-beingandexhilaration, lessened fatigue, andincreased talkativeness, energy and capacity for work. Those who got placebo did not report such effects. Nathanson believed that the drug would have wide therapeutic utility and might also be useful in preparing an individual for unusual expenditures of physical or mental energy. He cautioned that wider and longer experience is needed to consider the question of habituation and tolerance.

SUBJECTIVE EFFECTS AND THE EVOLUTION OF FORMAL SCREENING FOR ABUSE POTENTIAL

Prior to the turn of the 20th century, the problem of addiction to opiates, cocaine, alcohol, and certain sedatives was well recognized, but in most countries there were no specific statutes regulating availability of such

drugs. Assessments of drugs were generally informal, designed todevelop information for use by the profession and the public. The passage of international treaties controlling opium and cocaine, and subsequent passage of the Harrison Act in the United States, did not result in any immediate change in that situation. However, the development of formal programs for assessing the effects of drugs in order to predict their abuse potential, was a by-product of a deliberate effort to produce non-addictive substitutes for the various uses of morphine and related opiates. The effort was based on the assumption that oral codeine had a lower abuse liability than morphine, but was nevertheless a useful analgesic. This suggested that analgesic actions could be separated from the actions linked to abuse and dependence. In 1929, a committee of the National Academy of Science National Research Council, the Committee on Drug Addiction, formulated a strategy aimed at the development of nonaddicting therapeutic substitutes for morphine. As part of the strategy, two research units were formed, a chemical unit at the University of Virginia, and a pharmacological unit at the University of Michigan. These units worked in collaboration with a clinical research unit established within the United States Public Health Service, which in 1929 had been given responsibility for care of federal prisoners who were opiate addicts. A key figure in the development of the strategy and workings of the committee was Nathan Eddy. This program resulted in the development of a number of chemical entities which then needed to be evaluated by methods that were themselves still evolving.

As an opiate derivative, dihydromorphinone (Dilaudid) was controlled by federal laws at the time of its clinical introduction into the United States. But, it was reported to be a nonaddicting substitute for morphine. Eddy, in 1933, and King and coworkers, in 1935, reported that it produced and sustained physical dependence and had, therefore, addiction liability. Jasinski (1977) states that these were the "first evaluations of an agent primarily for the purpose of providing information important to the public health." Desomorphine, which had been prepared by Small at the chemical unit at the University of Virginia as part of the National Academy of Sciences program, did not produce physical dependence in monkeys (at least at the dosages used). Himmelsbach, however, demonstrated that the drug had morphinelike actions in morphine-dependent addicts and in nonaddict patients with chronic pain. On the basis of these findings, the Committee on Drug Addiction recommended, in 1935, that production or sale of desomorphine be prohibited in the United States. According to Jasinski (1977), this was the first instance in which "addiction liability" was a factor in the decision for narcotics control. However, it is worth

noting that the conclusions about dihydromorphinone and desomorphine were based exclusivelyon their capacity to suppress physical dependence, and not on their subjective or euphorigenic effects.

Meperidine, a chemical moeity unrelated to the opiate molecule, was initially synthesized in Germany and discovered to have analgesic actions. It was believed to have no addiction liability and was introduced into the United States in 1940. However, Himmelsbach (1942, 1943) reported that meperidine had an addiction liability similar to that of morphine. Since it was not an opiate, new legislation was required to include meperidine and its derivatives under the legal controls which applied to the opiates. Himmelsbach's conclusions about meperidine (Demerol) did not rely upon an assessment of its subjective effects, but, as with desomorphine, were based primarily on its capacity to suppress physical dependence. He did note in passing that patients "liked the effects of Demerol [which] were described as being like 'Nembutol or Cocaine"' (Himmelsbach 1943, p.6).

Although Himmelsbach tended to ignore those drug responses that could not be "measured," other researchers continued not only to take note of subjective responses, but to draw reasonably informed and sensible inferences from those responses. However, the methodology for such assessments had not yet reached current levels of sophistication. In a classic paper entitled, "A study of the analgesia, subjective depression and euphoria produced by morphine, heroine, dilaudid, and codeine in the normal human subject," Seevers and Pfeiffer (1936) gave detailed descriptions of their method for measuring analgesic thresholds using von Frey hairs, but their method for assessing subjective effects presented in its entirety is as follows: "During and following the experiment, the subject was asked to describe the subjective sensations resulting from the action of the drug." It should be noted, however, that the overall methodology of the study was otherwise relatively modem, and although placebos were not used, they did employ double-blind methodology and several drug dose levels.

Seevers and Pfeiffer (1936) reported that not one of their eight subjects "chosen for maturity and mental stability" because of the "remote possibility of addiction" evinced the slightest desire for repetition, rather "a hearty dislike for the procedure was generally expressed."

Although Seevers' and Pfeiffer's subjects did not wish to repeat the experience, neither did they necessarily find the effects of the drugs

unpleasant. When asked to report on euphoria (defined as akin to the stimulation ordinarily present during the first stages of alcohol intoxication), their subjects reported that heroin, morphine and dilaudid, in that order, produced the most pleasurable sensations, while very little euphoria was produced by codeine. Heroin was by far the most pleasant, and also produced the fewest adverse side effects. Seevers and Pfeiffer (1936) observed that "these very qualities which accord it first place, likewise render it most dangerous from the standpoint of addiction, since its action is rapid and intense, side actions are few, and euphoria often supplants subjective depression" (Seevers and Pfeiffer 1936, p. 184). (Curiously, these subjects, in contrast to confirmed addicts, reported that euphoria was less pronounced after intravenous than after subcutaneous administration, a difference which Seevers and Pfeiffer attributed to the effects of addiction and tolerance.)

These statements, which asserted that the addictive potential of opiates was directly related to their euphorigenic effects, were paraphrased in several standard pharmacology textbooks well into the 1950s (Lasagna et al., 1955; von Felsinger et al., 1955) and probably contributed to the widespread practice of underprescribing opiates for pain.

The following year, Seevers et al. (1937) reported on the subjective effects of three commonly used anesthetic gases. A significant finding was described as follows:

> . . . In nearly every instance, and with all agents, the subjects described what was termed the initial "jolt" which occurred one to three minutes after the first inhalation of concentrations high enough to produce significant analgesia. The promptness of occurrence of this intense subjective reaction following the use of these three agents is (a) cyclopropane, (b) nitrous oxide, (c) ethylene. Some subjects interpreted the sensation as an impending loss of consciousness and others in terms of euphoria. The maximum sensation usually lasts ten seconds to one minute and gradually becomes less pronounced, although the same concentration of the gas is continuously being inhaled. The time of this reaction did not in any instance coincide with the period of maximum analgesia. It is possible that the reaction is coincident with the time at which a high concentration of the agent first penetrates the nerve cell. It is interesting that the same general

> type of reaction occurs after the intravenous injection of the opiates and the time relationships are approximately the same.
> *Seevers et al., 1937, p. 296.*

It is, perhaps, an index of the relatively low level of public concern with drug abuse during this period that, despite these observations, there is no comment made on the possibility that these gases might someday be misused.

Up to this point, the process of assessing abuse potential continued to be based largely on Himmelsbach's original perspective that the habit-forming properties of opiates were due to and best predicted by their capacity to produce physical dependence. Not only did Himmelsbach give little weight to the subjective effects produced by the drugs being evaluated, but in his evaluation of physical dependence even subjective reports were largely ignored and only "measurable signs" were included in his method of rating the intensity of physical dependence. The major techniques used by the Lexington group well into the late 1940s, were direct induction of physical dependence, and substitution tests using either multiple or single doses of the test substance in subjects already dependent on morphine.

Some measure of the relative importance given at that time to the assessment of subjective effects may be inferred from the contents of a 1945 paper by Wikler, Goodell and Wolff titled, "The effects of analgesics on sensations other than pain." The drugs given included morphine, codeine, alcohol, aspirin, and a barbiturate; the study measured smell, hearing, touch, and vibration, but there was not a single comment on the subjective effects produced by any of the five drugs studied. A 1946 paper from the Lexington group (Williams et al., 1946) on marijuana and pyrahexyl compound contained a detailed description of effects on temperature, pulse, caloric intake, sleep, EEG, memory and even time estimation, but there were only three lines noting that exhilaration and euphoria were followed by general lassitude. The study used an observer's behavioral rating scale in which one dimension was mood; no mention is made of scales with which subjects could systematically report their own moods and feelings.

It was only after Isbell assumed leadership of the clinical research unit at Lexington that an effort was made to systematically measure some reflection of the subjective effects produced by the drugs being evaluated

by the laboratory. In 1947, Isbell and coworkers studied the addiction potential of methadone, another synthetic analgesic first developed in Germany, which had been introduced into the United States in 1945. In their evaluation of the effects of single doses of methadone, Isbell and coworkers (1948) concluded that it induced morphine-like physical dependence and suppressed morphine withdrawal, and that methadone was, therefore, a drug that should be controlled under narcotics laws. However, in these studies, they also concluded that it had euphorigenic effects similar to those of morphine, but the method by which they drew this inference was rather informal.

In a 1948 paper, Isbell stated that the pleasurable effects of drugs lead to their repeated use even before the development of physical dependence, and that detecting andmeasuringeuphoria was a critical aspect of assessing addiction liablity. He then described some of the behaviors which later became part of the standard method at Lexington for assessing opioidlike euphorigenic actions of drugs:

> ...The method used is simple: Single doses of the drug under test are administered to former morphine addicts, and the subjects are unobtrusively watched for a period of 6h or more by specially trained observers. For our purposes, euphoria is defined as a series of effects similar to those produced by morphine. These effects are: increased talkativeness, boasting, greater ease in the experimental situation, expression of satisfaction with the effects of the drug, requests for increased doses of the drug, increased motor activity, and, with larger doses, slurring of speech, motor ataxia, and evidence of marked sedation. As many experiments are done as are necessary to reach a clear-cut conclusion. The observations are controlled by administering 30 mg of morphine to the same subjects on other occasions. Initially, small subcutaneous doses of the drug under test are used, and if no untoward toxic effects are observed, the dosage is increased progressively in subsequent experiments until evidence of euphoria, roughly equivalent to that produced by 30 mg of morphine, is detected, or, if no evidence of euphoria is detected, the dosage is elevated until further increases would be regarded as dangerous. If euphoria is detected, blind experiments are arranged in which neither

> the subject nor the observer are aware whether the drug given was morphine or the compound under test. Finally, various doses of the drug are administered intravenously. *Isbell 1948.*

At this time, therefore, the emphasis remained on behaviors that observers could measure, rather than on systematic methods for obtaining reports from the subjects themselves.

Up to this point, the work on subjective effects of drugs had focused largely on opiate-like drugs. It is important to recognize that under the existing United States legislationonly opiates and their surrogates, cocaine, and (since 1937) cannabis were subject to special regulations. However, it was clearly recognized that these were not the only categories of drugs subject to abuse, or associated with physical dependence. Habitual use and withdrawal syndromes associated with barbiturate use were well recognized in the German medical literature in the 1920s, but the problem was less well appreciated in the American literature. In the introduction to their review, "Addiction to Analgesics and Barbiturates," Isbell and Fraser (1950) were able to state that a review of the literature on sedative dependence had not previously been done. Similarly, reports of amphetamine addiction began to appear in the medical literature in the 1940s.

At this time, the Food and Drug Administration (FDA) could require that information about the habit-forming properties of drugs be included in package inserts, but this fell far short of formal control of sale and manufacture. It was not until the passage of the Drug Control Amendments of 1965, that any governmental agency could regulate the manner in which sedatives, anxiolytics, stimulants (other than cocaine), and hallucinogens could be manufactured, sold or dispensed.

THE BLOSSOMINGS OF METHODOLOGY

The early moves by the Lexington group toward systematic assessment of subjective effects came just at the beginning of what we now recognize as the great flowering of psychopharmacological research. We would not wish to characterize that period as Golden Age, since it might imply that the present era was not even more vigorous and vibrant; but, it would not be inappropriate to point to the years between 1950 and 1970 as the tumultuous adolescence that leads into a mature and productive adulthood.

A number of confluent streams nourished a growing interest in methods for assessing subjective effects. Not the least of these was the number of new psychoactive drugs available for research and being introduced into clinical medicine (which, in those years, were often interchangeable concepts). The agents included new psychoactive drugs: nonbarbiturate sedatives, analgesic agents, stimulants, as well as the more exotic LSD and related compounds. By 1954, this stream had been joined by new drugs for treating psychiatric disorders: chlorpromazine, reserpine and meprobamate. In 1955, Himwich gave an address to the Society for Biologic Psychiatry in which he stated that his title, Prospects in Psvchopharmacology, could not have been chosen three years previously because the word did not exist. [Actually, Macht had used the term "psychopharmacology" in 1920, as had Thorner in 1935 (Caldwell 1970).]

Still another major contribution to the evolution of measurement was the work of Beecher and his colleagues at Harvard who deliberately set out to develop a laboratory for the measurement of subjective effects, for which they received a small grant from the Committee on Addictions in 1948. In a 1952 review, Beecher laid out the important principles for the systematic assessment of subjective effects; these included the use of the double-blind technique, placebo controls, randomization of drug presentation, appropriate choice of subjects (i.e., patients with illness or normal subjects), appropriate dosage levels, and sensitive methods that could detect drug action and increments in dose.

This was a time of rapid transition in the assessment of the abuse liability of drugs. In their 1950 review, Isbell and Fraser pointed out that definitions of addiction that equate it with physical dependence or make dependence the central feature are undesirable. They clearly endorsed Kolb's perspective that the critical issue is the capacity of the drug to produce pleasurable effects in a susceptible individual. While not disavowing the emphasis that Himmelsbach had placed on testing for physical dependence and on using only objective measures (i.e., ignoring what the subjects reported), the views of Isbell and Fraser were a further reaffirmation of Isbell's interest in euphoria expressed in his papers of 1947 and 1948.

But the assessment methods at Lexington did not immediately catch up with the shifting philosophical orientation. Fraser and Isbell wrote a paper comparing the reactions of postaddicts and normals to morphine. It described effectsonpupils, body temperature and respiration, but contained not a word on subjective effects. (Another evidence of bygone days: the paper was submitted to the *Journal of Phamacology and Experimental Therapeutics* on May 19, 1952 and appeared in August 1952.) If another paper was published on the subjective experiences of these subjects, we were unable to find it.

One of the classic studies carried out by the Harvard group compared the effects of morphine, heroin, and amphetamine in normal volunteers, postaddicts at Lexington, and chronically ill patients (Lasagna et al., 1955; von Felsinger et al., 1955). The study is noteworthy for a number of findings, but two stand out. First, in contrast to the "postaddicts" who liked the effects of morphine and heroin (experienced euphoria), the majority of normal volunteers found those drugs dysphoric. The normal volunteers did experience mood elevation and pleasant feelings after amphetamine. Second, this appears to have been the first study that used self-rating scales to measure the subjective effects of opiate drugs. The idea that the subjective response to a drug depended on the history and personality of the individual had been postulated and described previously by a number of workers (e.g., Kolb 1925; Lindemann and Malamud 1932), but not with the kind of supporting data found in these classic papers.

It is not clear if or why there was reluctance to utilize in some systematic way the verbal reports of the subjects at Lexington, but there was apparently an exchange of correspondence on the question, in 1956, between Beecher and Wikler. Beecher comments,

> There is a very great and understandable desire on the part of many people for objective indicators of subjective phenomena. Wikler hopes to find such in operational devices ...[W]ithout intheleast minimizing the importance of work in the areas mentioned, one wonders whether it is likely that the elaborate electronic methods referred to, however, will be any more helpful in measuring and understanding subjective responses than in the tail flick of a rat. . . . A cooperative statement by the subject must take first rank as an indication of the existence of a subjective response or of change in it.
> *Beecher 1959, p. 57.*

However, in 1956, Isbell and colleagues at the Addiction Research Center (ARC) published a paper on LSD-25 which made use of psychiatric interviews and of a questionnaire that had been developed by Abramson and coworkers the previous year. In 1957, Kometsky and his coworkers used this questionnaire to measure subjective effects of four drugs, including LSD and meperidine, in normal volunteers. However, these measures were not utilized in assessing dependence or abuse liability.

In 1961, a paper by Fraser and coworkers appeared that, as far as we can tell, represented the first use of the "single dose questionnaire for opiates," designed to evaluate quantitatively the attitude of opiate addicts toward opiate drugs and to find out what symptoms were experienced. The questionnaire had items to be completed by the observers (covering the behaviors mentioned by Isbell in 1948), but subjects were also asked, "Do you feel the medicine?"; to select from a list which drug they thought the test drug was most like; which of a number of sensations, (e.g., drive, sleepy, relaxed), they felt; and how much they liked the drug (Fraser et al., 1961).

By 1963, Hill and coworkers developed and published the Addiction Research Center Inventory (ARCI) containing several scales that were empirically demonstrated to be sensitive to the effects of a number of abused and non-abused drugs.

In recognizing the importance of subjective (euphorigenic) effects of drugs of abuse, in contrast to Himmelsbach's emphasis on physical dependence and measurable signs, Isbell was "rediscovering" the views of Lawrence Kolb, who had pioneered the U.S. Public Health Service's work in studying addicts. In 1925, Kolb, then at the U.S. Public Health Service Hygienic Laboratory in Washington, D.C. wrote:

> ... in referring to the mental pleasure of opium, a distinction should be made between the pleasure that is merely reflex following relief from anxiety and pain and the pleasure that results from raising an individual above his usual emotional plane... normal as well as abnormal persons may receive the first kind of pleasure, while only in rare instances, if at all, does any one except the emotionally unstable, the psychopath, or the neurotic receive the latter. The first, . . . may be termed negative pleasure; the second a relief from conditions that are more or less permanent or fundamental, may be termed positive pleasure. In persons who at first receive positive pleasure from an opiate and because of it continue the use of the drug until it becomes a physical necessity, the degree of the feeling wanes as more and more of the drug becomes necessary to satisfy the craving of physical addiction and to maintain comfort. It is the hope of reviving the pleasure in its original intensity that impels some psychopathic addicts gradually to increase the dose or

> to inject morphine or heroin directly into their veins . . . Amounts that at first gave unusual effects are then necessary to maintain what to an addict is normal functioning and to ward off discomfort . . . This is a poor substitute for the sense of ease and relief that the drug at first gave from the conflicts and tensions that are fundamental with the psychopath. It thus happens that the drug, taken in the beginning because of its power to raise an inferior individual above his normal level, must be taken in the end to keep him from sinking below it and to relieve conditions that the drug itself has produced.
> *Kolb, 1925, pg. 699.*

Kolb was not certain whether opiates could induce euphoria in normal individuals who did not have some special psychic vulnerability. He was astute in recording the experiences of opiate addicts and it is remarkable how closely these experiences are reflected in items that are now routinely used in scales that measure the subjective effects of opioids:

> The expressions that addicts make use of in describing their sensations illustrate better than anything else the mental pleasure that opium gives abnormal persons. At the same time they show the neurotic basis of addiction by indicating emotional conflicts or feelings of inadequacy, the relief from which is expressed as pleasure. The following are some of the common statements made:
>
> "It makes my troubles roll off my mind."
> "I do not have a care in the world."
> "It is exhilirating and soothing."
> "You do not care for anything and you feel happy."
> "You have a contented feeling and nothing worries you."
> "It stimulates you and makes you forget, so you don't care about anything."
> "It makes you drowsy and feel normal."
> "It causes exhiliration and a feeling of comfort."
> "A deadening, pleasurable effect."

There is a remarkable similarity between these statements and the items which make up the MBG scale of the ARCI.

Kolb went on to state:

> In addition to the mental pleasure produced by opium, some addicts receive a pleasurable physical thrill of short duration and varying intensity immediately following an injection of morphine or heroin . . . Most of them describe it as a feeling of warmth that quickly spreads through the abdomen following an injection . . . Striving for a repetition of it naturally leads to larger doses.
> *Kolb, 1925, p. 702.*

It is worth noting that Kolb's 1925 descriptions of the subjective effects of cocaine were as perceptive as his descriptions of the effects of opioids.

Still other influences on methodology were major technical advances in behavioral pharmacology. In the early 1960s Weeks, Schuster and Thompson; and Yanagita, Deneau and Seevers (see Schuster and Thompson 1969) independently developed techniques that allowed animals to self-administer drugs by the intravenous route. It was rather quickly shown that animals would self-administer opioids as well as other drugs at doses that were unlikely to be associated with significant physical dependence. Such findings further served to shift attention from measuring withdrawal syndromes to understanding the reinforcing effects of drugs and the relationship of these effects to abuse potential.

At this juncture, the early 1960s, events outside of science also began to influence the evolution of methodology. The United States was beginning to recognize that the non-medical use of drugs was becoming more widespread, and that the drugs being used were more diverse than at any time previously. There was widespread concern with growing use of marijuana, new concern with the much publicized use of LSD and psilocybin, as well as a belated recognition of the abuse of amphetamines and of barbiturates and non-barbiturate sedatives. Many states had regulated barbiturates, but without authority to control manufacture or shipments, widespread misuse persisted. These concerns led to the passage of the Drug Control Amendments of 1965 which gave FDA the authority to control the use of barbiturates, amphetamines and any drugs that the Secretary of Health, Education and Welfare (HEW) designates as subject to abuse (aimed at hallucinogens). However, even after the passage of these amendments, which by legislation specifically included the barbiturates and amphetamines, there remained considerable controversy

about which of the newer non-barbiturate sedatives ought to be regulated and what evidence of abuse potential was sufficient to justify regulation. Pharmaceutical firms that produced drugs like meprobamate and diazepam engaged in extended litigation to maintain an uncontrolled status for their products.

The Drug Control Amendments were short-lived. In response to the continued increase in the incidence of illicit drug use, and associated crime and social deviance, the federal government proposed new legislation. It was aimed at reducing the seeming chaos of interminable litigation over regulation of specific drugs under the Drug Control Amendments and the administrative confusion inherent in having two departments responsible for controlling drugs of abuse (HEW for barbiturates and amphetamines and hallucinogens and Justice for control of opiates, cocaine and cannabis). The new law, the Controlled Substances Act of 1970, shifted all enforcement to the Justice Department. However, the law made provision for scientific input on the issue of which drugs would require control, and, in an important precedent, recognized different degrees of risk which required different degrees of control. It also attempted to lay out specific objectives and criteria for judging the degree of risk of abuse. The assumption underlying this Act was that it was possible to obtain through research the kind of information needed to decide on what level of control was appropriate for any given psychoactive agent.

The legislation provided a further impetus to the development of methodology to assess the "abuse liability" of new psychoactive agents. For the most part, the core approach of most researchers was to determine the degree to which a new compound had properties comparable to one which was already judged to require control, i.e., was already included in one of the five schedules of the Controlled Substances Act. However, the legislation did not clarify in any way how different aspects of a drug's action should be weighed in reaching an overall judgement on the degree of abuse liability or addiction potential of a given drug.

The problem of amphetamine illustrates this point. Cases described as addiction to amphetamines began appearing in the U.S. medical literature as early as 1940. Yet, in a classic review of the amphetamines in 1966, Kalant could still write:

> Although a great deal has been written about whether or not amphetamines are addictive drugs, there is as yet no consensus on this very important point. This has been due partly to lack of well-documented evidence, but to a far greater extent to the disagreement over what constitutes

> addiction. The crux of the disagreement has been whether or not amphetimines(sic), when consumed chronically, produce physical dependence as manifested by the presence of clear-cut withdrawal symptoms and, therefore, strong craving. Thus, authors who have based their judgment almost exclusively on the question of physical dependence have argued that amphetamines do not produce addiction. Other authors, who have attached greater importance to such factors as compulsion to continue to take the drugs, development of tolerance, and harmful effects, have drawn the opposite conclusion . . . in the pertinent literature value judgments are clearly implicit, to the effect that addiction, if proven, would condemn these drugs as bad, whereas a verdict of habituation, dependence, or abuse would largely exonerate the drugs but condemn the habitues, dependents, or abusers. The discussion therefore seems to hinge on the identity of the culprit: the drug or its user . . .
> *Kalant 1966, p. 77.*

Kalant was, in one sense, restating the arguments of Isbell and Fraser (1950).

Despite knowledge of what we now refer to as the post World War II epidemic of amphetamine addiction in Japan, many workers continued to make a clear-cut withdrawal syndrome the sine qua non for defining addiction. Again, we see the ghost of John Jones arguing with his countryman and fellow pharmacist, John Awsiter. There appears to be something exceedingly seductive about the very idea of identifying some measurable withdrawal syndrome and attributing to this syndrome the entire responsibility for the dependence process, (or at least the bulk of the responsibility). Implicit in this seductive idea is the perspective that drugs that induce only subjective changes, but not physical dependence, represent lesser hazards for those who use them and for society as a whole.

The same issues can be identified when we consider the history of assessing the abuse liability of sedatives and anxiolytics. The initial studies of barbiturate drugs by Isbell et al. (1950) and Fraser et al. (1954) focused on the effects of chronic intoxication and the barbiturate withdrawal syndrome. The descriptions of the effects of chronic intoxication remain classics, but it was not until a decade later that Martin et al. (1962, 1974) used questionnaires to demonstrate that non-tolerant opiate addicts “liked”

the effects of pentobarbital. But studies also showed that not all varieties of liking are the same; i.e., the subjective effects of barbiturates although "liked" were distinct from those of opiates and were distinct from the subjective effects of LSD and cannabis-like drugs as well (Hill et al., 1963; Haertzen 1966). Studies at the ARC also showed that phenobarbital, which was known to induce physical dependence and suppress withdrawal from short-acting barbiturates was far less potent than pentobarbital in inducing euphoria, as measured by the ARCI.

The relatively low abuse potential of phenobarbital, which had been available for more than 60 years, led a panel of experts to conclude, in 1969, that direct addiction studies alone could not predict abuse potential, but that other tests, such as the capacity of single doses to induce euphoria, might be needed (Fraser and Jasinski 1977). Such assessment would presumably result in a judgement that shorter-acting barbiturates, such as pentobarbital, which induces both acute subjective effects and physical dependence, require more regulation than phenobarbital, which is associated primarily with physical dependence.

However reasonable these principles may be, problems have arisen in their application to the regulation of the more than twenty available benzodiazepine congeners, agents which differ widely in terms of their acute subjective effects and pharmacokinetic properties (and, therefore, the onset and intensity of their withdrawal syndromes). Given their currency, these issues are probably best excluded from an historical review.

EUPHORIA'S PRIMACY DOUBTED

The notion that euphorigenic effects can usefully predict abuse liability, has been criticized by some workers because it has not explained enough and because it has diverted attention from other important scientific questions. These criticisms have been succinctly expressed by Peter Dews.

> ... it was supposed that the prediction of addiction liability was essentially equivalent to prediction of euphorigenic power. As with most self-evident ideas, the mere matter of there being essentially no evidence in favor of it, and much against it, had little effect on its acceptance. Addicts did not talk much of exquisite pleasure, even when words were put in their mouths; mostly they talk of no more than a transient

> thrill. The types of effects caused by heroin, alcohol, amphetamines, and tobacco smoking are so grossly different that no one has ever identified a common factor in the effects of all the drugs, euphoria, that causes them all to be abused. The effects of tobacco smoking are ordinarily so subtle that a CNS effect is not detectable, yet smoking is as compulsive a habit as any.
>
> The euphoria notion has been disposed of many times and few here today would subscribe explicitly to a simple euphoria theory of drug abuse. We know too much about the enormous role of external circumstances in determining whether an individual will take drugs or not, and if so, which drugs, for us to try to pin all the responsibility for abuse on an intrinsic euphoriant property of the drug...
> *Dews 1977, p.75.*

THE STRUGGLE UNRESOLVED

The ghost of John Jones may still haunt the dwelling places of government and academia. Let us consider the case of buprenorphine. This is a fascinating drug derived from thebaine and closely resembling etorphine, one of the most potent opioids known. Buprenorphine is a potent analgesic. At early stages of testing, it appeared to produce little physical dependence in rats and monkeys; it did so in the dog; and it also suppressed morphine abstinence. It is self-administered by animals trained to inject opioids. Properly given, it can substitute for morphine in subjects maintained on low doses of morphine, and it can induce morphine-like euphoria. Despite these properties, buprenorphiie has been available in a number of countries for several years with no controls other than the need for a physician's prescription. But for an appeal by the Drug Enforcement Administration (DEA), the drug would have also been made available in the United States without being subject to controls under the Controlled Substances Act.

What considerations went into the various administrative and regulatory decisions? Buprenorphine was tested for its abuse potential at the Addiction Research Center at Lexington in 1975 and 1976 and the results were published by Jasinski et al. in 1978. It was believed to be a partial Mu agonist because, in the dog, single doses exhibited ceiling effects, and

could, under some circumstances, precipitate abstinence. Buprenorphine was given subcutaneously in doses up to 2 mg to 14 postaddicts.

> In single doses, buprenorphine produced typical morphinelike effects. Subjects and observers identified it predominantly as an opiate . . . it was a "euphoriant" as indicated by the significant scores on scales that measure euphoria - 'liking' and morphine-"Benzedrine" group (MBG) scale scores.
> *Jasinski et al., 1978.*

Its effects appear to persist longer than those of morphine, similar to what is observed with methadone. Relative to morphine, it appeared to be more potent in constricting pupils than in inducing subjective effects. In the doses used (up to 2.0 mg) ceiling effects were not demonstrated. In a direct addiction study where dosage was 8 mg/day, five subjects and observers identified the drug as morphine-like. Only three subjects completed the double blind withdrawal component of the 58 day study. As compared with data previously gathered by Fraser et al. (1961), the Himmelsbach scores for these subjects exceeded placebo levels, peaking on the 15th day of the withdrawal. For the first 10 days, the withdrawal scores were significantly smaller than scores observed with other subjects previously withdrawn from morphine, cyclazocine, nalbuphine, pentazocine, or butorphanol. On day 14, two of the three subjects experienced typical signs and symptoms of morphine withdrawal. Morphine was given to alleviate withdrawal on days 15 to 20. It was concluded that abrupt buprenorphine withdrawal (which could not be precipitated with up to 4 mg of naloxone) was associated with mild withdrawal of delayed onset. A study of the morphine blockade in five subjects indicated that, after chronic treatment, buprenorphine attenuates the effects of up to 120 mg doses of morphine, an effect which persists for at least 30 hours after buprenorphine administration. (It should be noted that a similar "blockade" of the effects of injected opioids was reported for subjects maintained on 80 to 100 mg of methadone by Dole and Nyswander in 1965).

For reasons not entirely clear, the conclusions drawn from the data were that buprenorphine produced morphine-like euphorigenic effects which would not exceed those of a 20 to 30 mg parenteral dose of morphine, and that given the relatively delayed and mild abstinence syndrome (which might be expected to be less intense than from maximal doses of codeine or propoxyphene), buprenorphine was "judged to have a significantly

lesser abuse potential than codeine or propoxyphene." Since it is not easy to argue that an effect equivalent to 20 to 30 mg of parenteral morphine would not have some abuse potential in susceptible populations, the lesser abuse potential predicted for buprenorphine must rest largely upon other grounds. In this case, these grounds would appear to be either its status as a partial Mu agonist, or its delayed and attenuated morphine-like withdrawal syndrome.

In making this complex judgement, we encounter again these two central notions about the nature of drug abuse and dependence: the euphoric or reinforcing effects vs the avoidance of withdrawal; John Jones vs John Awsiter; Lawrence Kolb vs Clifton Himmelsbach. The conclusion about the lower abuse potential of buprenorphine is probably true - for patients being treated for pain. However, in the past few years, there have been reports from several countries of the misuse of buprenorphine by heroin addicts. (see O'Connor et al., 1988).

The marketplace, and the behavior of susceptible populations - the gold standard against which all of laboratory predictions must be measured - now seems to be telling us that John Awsiter and Lawrence Kolb were probably closer to the mark: that provided a drug is not toxic, significant opioidlike subjective effects, rather than severity of physical dependence, is the better predictor of potential for misuse by certain vulnerable populations.

Admittedly, as has always been the case, such a conclusion makes it more difficult to draw the distinction between moral failure and medical disorder, between sin and self-medication.

Perhaps the problem is that we have been trying to answer a question that cannot be answered in the way that it is framed. It may be that John Jones and John Awsiter are both right with respect to the risk for different populations. For the patient who is given a drug for therapeutic purposes - whether an analgesic or an anxiolytic, the euphorigenic effects may pose little hazard, but the capacity of the drug to engender a form of physical dependence with an aversive withdrawal syndrome may very well lead to a perpetuation of drug use beyond the time when it is medically indicated. On the other hand, for those with a predisposition to seek drug-induced mood change, (a group that needs to be further defined), especially the state which we loosely describe as "euphoria," it is the capacity of a drug to induce such change that predicts its misuse when it becomes available to those individuals. To try to average these two distinct categories of risk

leads both to an overestimation of risk for some and an underestimation of risk for others. If we add still another criterion to estimate abuse potential, such as the capacity of the drug to cause problems when ingested for suicidal or homicidal purposes, we risk the creationof a rating that conveys no meaning at all with respect to problems of drug dependence and abuse. In an historical review, however, weshouldnote that, in nineteenth century England, the use of opiates for such purposes was an important reason given for the effort to restrict their availability, a reason which antedated widespread concern about its habitual or "stimulant" use (Berridge and Edwards 1981).

CONCLUSIONS

How far have we come in the 3,000 or so years since the sages of the Bible warned us that the pleasurable effects of wine could lead us into excessive use, mischief and misfortune? If we measure progress by methodological sophistication, we have made great strides. We have learned to use placebos, to select appropriate populations for study, to control for sequence of drug-administration, and for expectations on the part of both subjects and observers, to use a range of doses, to frame our questions carefully, to develop reliable scales, to use appropriate statistical analyses, and to be cautious in extrapolating our findings only to populations similar to our subjects. However, if we measure progress by how far we have come in understanding just how drugs induce euphoria, or why the use of euphorigenic drugs so often leads to abuse, especially in certain susceptible individuals, our progress has been modest. We now know that a wide range of pharmacological agents can induce euphoria or generally pleasant subjective states in humans, and that several animal species will self-administer drugs that people tell us induce euphoria; that is, the same drugs are reinforcers. (Among the obvious discrepancies in this domain are those cases where animals do not self-administer a drug, such as cannabis, which in humans produces euphoria with considerable reliability.) We are also learning that in laboratories certain individuals will continue to self-administer drugs at dose levels which do not result in self-reported subjective changes.

We also know that there is more than one kind of physical dependence. To some degree, we are now beginning to appreciate that, as counterintuitive as it may seem to some, physical dependence in its broadest sense is not the same as drug dependence, and that only some withdrawal

syndromes are associated with intense drug seeking behavior - a point that one of us has tried to make without a great deal of success for more than 20 years (Jaffe 1965, 1985). In researching this paper, we discovered that these same points had been made by Isbell and Fraser in their 1950 review.

It may be that it is our own need to be able to point to some visible, concrete measurement of altered body function associated with intense, repetitive drug-using behavior that leads us again and again to place great emphasis on withdrawal syndromes. Whether we do this so that we can more easily explain the behavior to those who see it in moral (rather than behavioral, biological or medical) terms, or we do it because we really do not trust the findings from studies of subjective effects, is not clear.

New definitions of drug dependence included in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) have attempted to correct the balance by emphasizing the notion that drug dependence varies in intensity, and that it is best defined by the behaviors that people exhibit and the degree to which the drugs control behavior, rather than the degree to which they experience withdrawal symptoms when the drugs are stopped. On the whole we are probably now reasonably advanced in our capacity to predict from our laboratory studies which drugs will be abused (at least by some) if they were to become widely available.

Where we may have made the least progress is in our methods for integrating all the knowledge we can generate about any given drug and translating it consistently into control policies that balance the public's need for the drug as a therapeutic agent against the risks that some members of that public may misuse it.

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CHAPTER 5

Human Abuse Liability Assessment by Measurement of Subjective and Physiological Effects

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INTRODUCTION

For nearly three decades, measurement of subjective and physiologic drug effects has been the cornerstone of abuse liability testing of new chemicals or new formulations considered for use in therapeutics. The purpose of this paper is to describe this testing strategy. While it is not within the scope of the chapter to thoroughly review the historical development of subjective effects assessment procedures (see Jaffe and Jaffe, in this volume, for such a review), knowledge of certain antecedents is critical to understanding the rational basis for conducting this type of abuse liability testing as well as for appropriate interpretation of data.

The underlying principles of using subjective and physiologic response measures to predict abuse liability of substances evolved from basic research into the addictive process with opioids. These principles are (1) that subjective effects can be quantitatively assessed, (2) that subjective responses to drug administration can often be used to predict the reinforcing actions of drugs, and (3) that subjective and physiologic responses following drug administration reflect specific drug-induced alterations in human brain and body function (see discussions in Jasinski 1977; Schuster et al., 1981; USDHHS 1988).

Several strategies are used to predict if a drug will readily sustain patterns of abuse. These include studies designed primarily to assess tolerance, physical dependence, discriminative effects, and reinforcing efficacy, utilizing both animal and human subjects (see other chapters in this volume, Goldberg and Hoffmeister 1971; Thompson and Unna 1977; Thompson and Johanson 1981; Brady and Lukas 1984; Bozarth 1987; USDHHS 1988). Studies of subjective and physiologic effects provide data which are complementary to the data obtained from the aforementioned study strategies. Taken together, these various strategies of evaluation provide a more thorough characterization of a drug. The confidence in decisions

regarding abuse liability is increased when convergent results are obtained using several such methodologies.

The present chapter focuses on the methods to evaluate the efficacy of drugs in the production of transient alterations in self-reported mood, feeling, thinking, and perception, which lead to their self-administration; that is, subjective drug effects. Certain physiologic drug effects that are often used in such studies will also be discussed.

BACKGROUND

The production of certain subjective effects essentially defines dependence producing drugs and sets them apart from other drugs and food; drugs that produce such effects are sometimes termed "psychoactive," "psychotropic" or 'behaviorally active;" the effects are often referred to as "psychoactive," "interoceptive," "subjective," "psychic," or "self-reported" (President's Advisory Commission on Narcotic and Drug Abuse 1963; WHO 1981; USDHHS, 1988). Dependence producing drugs are chemicals that can readily control behavior by a variety of potential mechanisms (Thompson and Schuster 1968; USDHHS 1988). For example, they may serve as positive reinforcers by virtue of direct actions in the central nervous system, they may produce desirable changes in mood and feeling, they may relieve dysphoric mood states, they may alleviate pain and other physical ailments, their administration may facilitate performance which may otherwise have suffered due to fatigue or stress, and repeated administration can lead to a state of physical dependence whereby abstinence is accompanied by an increased propensity to take the drug. Similarly, the potential abuse liability of drugs can be assessed by a variety of procedures. However, until at least the 1970s, in human subjects, quantification of subjective effects was the only validated method of testing for the likelihood that use of a drug would lead to addictive patterns of use. Since then, drug self-administration and drug discrimination testing strategies developed using animals as subjects (e.g., Thompson and Unna 1977) have been incorporated into human abuse liability testing studies (Bozarth 1987; USDHHS 1988).

The theoretical basis for the assessment of subjective drug effects had been understood early in the twentieth century. For example, in the 1920s, Lewin had observed that it was the "phantastica" (i.e., "subjective") effects of substances that lead to their habitual use (Lewin 1931). Practically useful methods for evaluating such effects did not emerge until the behavioral sciences themselves had become sufficiently sophisticated in the 1930s and 1940s. Prior to this tune, dependence

producing drugs were identified primarily on the basis of retrospective observations of their effects in clinical and social settings.

The systematic assessment of subjective drug effects was essentially an extension of the methods developed to assess physiologic actions of drugs. By the late 1940s, several drug dependence researchers had recognized that physical dependence potential testing was of limited value in predicting the likelihood that behavioral dependence would develop following exposure to a given drug (Isbell 1948; Isbell and Vogel 1948). These researchers used observational techniques to infer interoceptive drug effects. "Euphoria" was the designated label for such effects; drugs producing such effects were sometimes termed "euphoriants". The rationale and basic methods of assessment were most elegantly described by Isbell (1948):

> Since most people begin the use of drugs andbecome addicted because the drugs produce effects which they regard as pleasurable, the detection of euphoria is a very important procedure in evaluating abuse liability. The method used is simple: single doses of the drug under test are administered to former drug abusers, and the subjects are unobtrusively watched for a period of 6 hours or more by specially trained observers. For our purposes, euphoria is defined as a series of effects similar to those produced by morphine. These effects are: increased talkativeness, boasting, greater ease in the experimental situation, expression of satisfaction with the effects of the drug, requests for increased doses of the drug, increased motor activity, and, with larger doses slurring of speech, motor ataxia, and evidence of marked sedation. As many experiments are done as necessary to reach a clear-cut conclusion. The observations are controlled by administering 30 mg of morphine to the same subjects on other occasions. Initially, small subcutaneous doses of the drug under test are used, and if no untoward toxic effects are observed, the dosage is increased progressively in subsequent experiments until evidence of euphoria, roughly equivalent to that produced by 30 mg of morphine is detected or if no evidence of euphoria is detected, the dosage is elevated until further increases would be regarded asdangerous. If euphoria is detected, blind experiments are arranged in which neither the subject nor the observer are aware whether the drug given was morphine or the compound under test. Finally various doses of the drug are administered intravenously.

It is noteworthy that the initial definition of euphoria was judged solely by observed signs, that the data were exclusively those that could be collected by observers, and that the model was based on the effects of morphine. Subsequent theoreticians occasionally assumed that subjective effects (viz. euphoria) were causal in the maintenance of drug seeking behavior. The more widely accepted current position would seem to be that, subjective effects are related to the maintenance of and relapse to drug seeking in a complex but orderly manner but are not necessary in the causation of the behavior (see discussion in Schuster et al., 1981).

Evolution of the methods of Isbell, and their practical implementation, was greatly enhanced by developments in the 1950s and early 1960s. For example, Rao (1952) developed procedures for assessing changes in subjective state which were of substantially enhanced reliability, and Beecherand his colleagues (Beecher 1959) adapted quantitative bioassay procedures to assess subjective responses to pain stimuli and to the effects of analgesic drugs on such responses (Jasinski 1977; USDHHS 1988). Beecher alsoestablished the importance and utility of the crossover (within subjects) experimental design with inclusion of standard and placebo drug control procedures, the double-blind technique, and randomized testing sequences in the assessment of subjective drug effects.

These pioneers in the assessment of abuse potential of drugs made the following observations that provide the conceptual basis of current strategies:

1) drugs produce reproducible transitory subjective states,
2) states produced by drugs may be used to define drug classes,
3) individuals can reliably discriminate drug induced subjective states,
4) the subjective state characteristic of drugs of abuse is one of euphoria,
5) the nature of the state is related to the propensity to take the drug,
6) physical dependence is neither necessary nor sufficient to establish and maintain drug seeking behavior (cf. Jasinski 1977; USDHHS 1988).

Development of the Single Dose Questionnaire (SDQ) and the Addiction Research Center Inventory (ARCI)

The advances described above contributed to the development of what is generally considered the first standardized questionnaire used to compare the addictive properties of a wide range of drugs, namely the Single Dose Questionnaire (SDQ) (Appendix A). The SDQ was developed by Fraser

and his colleagues as an extension of the methods of Himmelsbach to quantitate transient changes in mood and subjective state induced by the administration or withdrawal of drugs (Fraser and Isbell 1960; Fraser et al., 1961). The SDQ was comprised of scales that permitted the subject to report feeling or not feeling the drug, to identify it from a list of possible drugs, to report symptomology, and to rate any liking of it. An analogous questionnaire, for completion by observers, permitted independent verification of certain self-reported effects (Appendix A). The designation, Single Dose Questionnaire, was derived from its applicability to the qualitative and quantitative characterization of drugs based upon the individual administration of drugs to human volunteers.

The next major advance in the quantification of subjective drug effects was the development of the Addiction Research Center Inventory (ARCI) by Haertzen and his colleagues (Haertzen et al., 1963; Haertzen 1966, 1974; Haertzen and Hooks 1969; Haertzen and Hickey 1987) (Appendix B presents a short form of the ARCI). The ARCI contained scales that were empirically derived to be sensitive to the effects of specific drugs and drug classes (e.g., sedatives, stimulants, hallucinogens). One of the most useful scales was developed to measure the effects of morphine and benzedrine (a prototypic opioid and amphetamine, respectively); this scale was subsequently referred to as the "Morphine Benzedrine Group" or "MBG" or "Euphoriant" scale since morphine-like and benzedrine-like drugs increase the scale scores while simultaneously producing feelings often reported as pleasurable (Haertzen et al., 1963; Haertzen 1974). Scores on the MBG scale are also elevated by most other addicting drugs (Jasinski 1977; Jasinski et al., 1984).

Determination of pharmacologic equivalence

The SDQ and ARCI tests were standardized by administering them to volunteers following their exposure to placebo or to some dose of a drug that was already known to be widely abused or otherwise used by drug addicts. These included morphine, amphetamine, pentobarbital, alcohol, marijuana, and lysergic acid diethylamide. Subsequently, drugs such as diazepam and nicotine were also tested. These drugs each served to some degree as prototypic or standard drugs since each produced its own unique profileof actions. Assessing the abuse liability of new drugs is essentially a procedure for assessing their pharmacologic equivalence with the standard drugs.

The method of classification by comparing new substances to prototypes was not only important for pharmacological theory and clinical utility; it was also the basis for legal/regulatory actions. In 1946, the Harrison

Licensing Act was amended to subject substances with addiction-forming or addiction-sustaining liability similar to that of morphine to narcotics control laws (Martin 1977). This action paved the way for the Narcotics Manufacturing Act of 1960 to regulate substances with "addiction-sustaining liability similar to morphine or cocaine...," and, in turn, to the Comprehensive Drug Abuse Prevention and Control Act of 1970. The latter Act provided for various levels of restriction of manufacturing, access, sale, and use of substances (i.e., Schedules I-V) depending, not upon their chemical structure, but rather upon their degree of pharmacologic equivalence to various prototypic addicting drugs (Martin 1977).

To the extent to which certain common features are identified, they may be categorized together, e.g., as dependence producing or addicting drugs. Furthermore, to the extent to which the drugs differ in certain respects, they may be subcategorized as, for example, dependence producing drugs of the morphine type or of the amphetamine type. Such categorization must be viewed with caution, however, since overemphasis on any particular feature of a drug can be misleading. For instance, nicotine has been viewed as both a stimulant ("excitant") (Lewin 1931) and a sedative (Armstrong-Jones 1927). Most commonly, nicotine is now categorized as more stimulant-like than sedative-like, but with an appreciation of its diverse range of potential effects (Gilman et al., 1985).

It is now well-established that if a drug is discriminated and produces elevations on the liking scale of the SDQ, and if it produces elevations on scores on the MBG scale of the ARCI, then it is appropriately categorized as a drug with a potential to addict users. Two other scales of the ARCI are commonly used to characterize the subjective effects of psychoactive drugs in humans. These are the Pentobarbital Chlorpromazine Alcohol Group (PCAG) Scale which reflects sedation and intoxication, and the Lysergic Acid Diethylamide (LSD) scale which reflects dysphoria and feelings of fear and paranoia (Haertzen 1974). A drug identification scale and symptom check list of the SDQ provide additional information characterizing the subjective effects of the drug and providing an objective basis for its classification.

The selectivity and sensitivity of such procedures is illustrated in figure 1. As shown in the figure, when persons with multiple addiction histories were given drugs under double-blind conditions, they rated placebo and the nonaddicting zomepirac at a minimal level of "liking." As a direct function of dose, however, the known addicting drugs were rated with greater liking scores. Pretreatment with opioid antagonists blocks such effects produced by morphine (Jasinski 1977) and pretreatment with a

nicotinic antagonist blocked such effects produced by nicotine (Henningfield et al., 1984).

Using the MCI, a finer grain analysis of the subjective effect is possible. For example, table 1 shows the profiles of some prototypic drugs obtained on commonly used scales of the ARCI. As shown in the table, all of the known addicting drugs produced changes in mood and feeling that

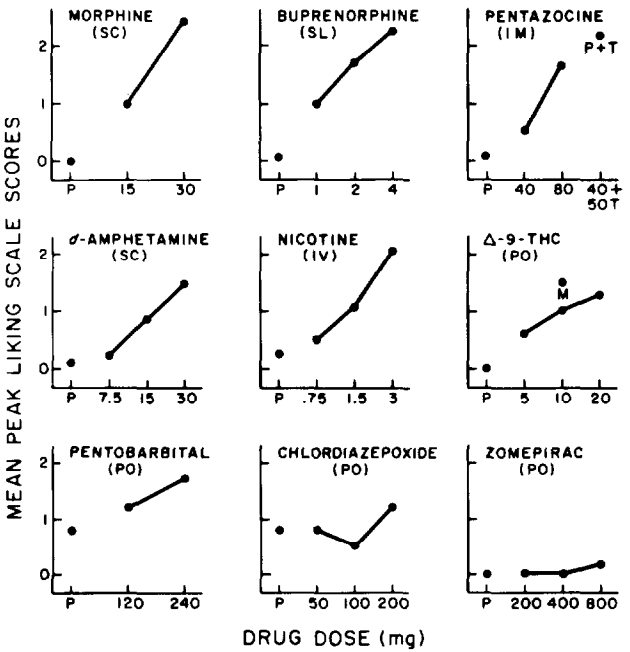

Figure 1: Mean scores on the Liking Scale of the Single Dose Questionnaire from subjects tested at the Addiction Research Center. The number of subjects in each group range from 6 (pentobarbital and chlordiazepoxide) to 13 (d-amphetamine). The high dose of each drug except zomepirac produced significant ($p < 0.05$) increases in scores above placebo data. The responses are peak responses which occurred after the drug had been given. The time of the peak response ranged from about 1 minute (nicotine) to 5 hours (buprenorphine). Morphineandzomepirac data are from the same group of subjects as are the pentobarbital and chlordiazepoxide data. The P+T point on the pentazocine graph is the score, by the same subjects, to 40 mg pentazocine given in combination with 50 mg tripelennamine (an antihistamine thatproduceda Liking score of 0.9)—the street combination called "T's and Blue's." The Mpoint on the Δ⁹-THC graph is the score, from the same subjects, obtained after smoking a marijuana cigarette that contained 10 mg (1 percent by weight) Δ⁹-THC. (from Jasinski, Johnson, and Henningfeld 1984).

Table 1. Drug-induced increases (+) and decreases (-) on ARCI scales. Investigators' Estimates: -- - -0 0 0+ + ++

Drug Condition	Ef	MBG	PCAG	LSD	SOW
Stimulants-amphetamine, cocaine	+	++	0	0+	0
Opiates-heroin, morphine, methadone	0	++	0+	0	0
Partial opiate agonists—pentazocine, nalbuphine	-	+	+	+	0
Marijuana	-0	++	0+	+	0
Barbiturates—pentobarbital, secobarbital	-0	+	++	0	0
Minor tranquilizers—diazepam	-0	+0	++	0	0
Alcohol	-	+	++	0	0
Major tranquilizers—chlorpromazine	-	0	++	0	0
Narcotic antagonists—nalorphine, cyclazocine	-	0	++	+	+
Hallucinogens—LSD	-	+	0	++	+
Others—scopolamine	—	0	++	+	+
Inactive—zomepirac, loperamide, bupropion		0	0	0	
Opiate withdrawal—morphine, heroin, methadone	-	-	++	+	+++
Alcohol withdrawal	—	-	++	+	++
[1]Simulated barbiturate withdrawal	—	-	++	++	+++
Simulated alcohol withdrawal	—	—	++	++	+++
Simulated opiate withdrawal	—	-	++	++	+++
Simulated pep pill come down	—	-	++	++	++
Simulated cocaine come down	—	-	++	++	++

Note: from Haertzen and Hicky 1987.
[1]Test results based upon retrospective reporting of subjective effects.
EF = Efficiency or BG (Benzedrine group variability)
MBG = Morphine-Benzedrine group
PCAG = Pentobarbital, chlorpromazine, and alcohol group
LSD = LSD group or drug correction
SOW = Strong opiate withdrawal

resembled those produced by morphine or benzedrine enough to significantly elevate the MBG scale scores.

Validation of measures

These self-reported markers of drug effects associated with their abuse liability have been validated by the use of similar rating scales by observers who are blind as to the condition. Based on their observation of the behavior of the subjects, observers can provide similar dose-related increases in scores on strength of the drug effect and/or the level of drug liking for alcohol (Henningfield et al., 1984), pentobarbital (Martin et al., 1974), morphine and heroin (Martin and Fraser 1961), amphetamine (Jasinski and Nutt 1972), either i.v. nicotine or research cigarettes which varied in nicotine delivery (Henningfield et al., 1985), and a variety of other drugs (Jasinski 1977).

These self-reported indices of abuse liability also correspond to a variety of physiologic effects that can be approximately simultaneously measured. Some of these physiologic changes vary across drug class; for example, pupil diameter increases appear to correspond to early nicotine-induced subjective effects (Henningfield et al., 1984); whereas pupil diameter decreases when morphine is given (Jasinski 1977). Other physiologic effects show a greater degree of similarity across drug classes: for example, studies of ethanol administration in human subjects revealed that paroxysmal bursts of electroencephalogram (EEG) alpha activity paralleled subjective reports of euphoria during the ascending limb of the plasma ethanol curve (Lukas et al., 1985a, 1986a) which also paralleled increases in plasma adrenocorticotropic hormone (ACTH) levels (Lukas and Mendelson 1988). Similar effects were observed following marijuana smoking (Lukas et al. 1985b, 1986b) and acute i.v. nicotine administration (Lukas and Jasinski 1983). In turn, similar changes in EEG alpha activity have been shown to correspond with subject-reported pleasurable states which can occur in the absence of drug administration (Lindsley 1952; Brown 1970; Wallace 1970; Matejcek 1982).

Physiologic data, obtained in the course of abuse liability assessment studies, serve at least three distinct and important functions. First, physiologic data provide an independent and objective means of verification of exposure to the drug and of the degree of dose sensitivity of the subjects. Second, physiologic data provide information regarding the possible toxicity of the drug. Third, physiologic data may reveal mechanisms, or at least, concommitants of drug induced changes in subjective effects.

MEASUREMENT TECHNIQUES

Early on, it was recognized that reconciliation of clinical reports and anecdotal observations with scientific theories of drug addiction could best be accomplished through the careful observation of human volunteers in a controlled research setting. In such settings, drugs could be administered or withdrawn and resulting phenomena recorded, thus revealing the oftentimes complex relationships among independent and dependent variables.

Current methods for assessing subjective and physiologic drug effects essentially entail giving either drug or placebo to a volunteer, and then asking him/her to report the nature of effects produced. Replicability and objectivity are increased by using standardized questionnaires such as those described above (e.g., "liking" scales, ARCI). In practice, several procedural variations are used to further enhance the reliability and validity of the results. The dose of the drug is varied to assess the nature of the dose-effect relations; for all dependence producing drugs, ratings of dose strength, or percentage of accurate drug identifications, are directly related to the dose given. Subjects with histories of use of a variety of drugs can be asked to report which, if any, of those drugs, the test drug feels like. Table 2 provides a summary of the basic methods of assessing subjective and physiologic effects in abuse liability studies.

LIMITS OF USING SUBJECTIVE EFFECTS DATA TO PREDICT ABUSE LIABILITY

The main constraint of using subjective effects assessment to predict actual patterns of drug abuse is that such testing does not assess the wide range of nonpharmacologic factors that may function to increase or decrease the actual abuse and associated public health problems. For example, use of even highly addictive substances such as heroin, cocaine, and tobacco products have historically varied as a function of factors such as price, availability, social acceptability, and public knowledge of health risks (cf. USDHHS 1988).

Hallucinogens provide a notable category of substances in which patterns of abuse have appeared to be particularly related to social factors (USDHHS 1988). Interestingly, these drugs tend to robustly increase reports of items on the ARCI LSD scale that are often related to feelings of fear,

Table 2. Basic methods for assessing subjective drug effects.

(1)	Subjects are tested in a controlled laboratory setting with appropriate medical support and with formal procedures to protect their rights and welfare.
(2)	Subjects are volunteers with histories of use of a variety of drugs; such subjects can accurately discriminate substances with a potential for addiction.
(3)	To minimize possible bias, the subject and, ideally, the experimenter, are kept blind as to whether drug or placebo were given, and possibly what type of drug might be given
(4)	Single doses of drugs are given at sufficient time intervals to eliminate residual drug effects. Intervals range from about one hour to several days
(5)	Following the drug administration, a variety of physiological, observer-reported (signs or behaviors) and self-reported (symptoms or subjective) effects are assessed at intervals which range from a few seconds to several hours, depending on the time course of drug action. When possible, simultaneous assessment of blood levels of the drug can provide information relating the pharmacokinetics of the drug to the subjective and physiologic effects.
(6)	The test compound is always compared to placebo, and usually to an appropriate positive control (such as morphine in a study of analgesics, or pentobarbital in a study of sedatives).
(7)	Both the test and control compounds are given at two or more dose levels. A limited number of subjects (usually about 10) participate according to a design whereby the subject is tested under each condition (cross-over or within-subject design).
(8)	Pretreatment with a known blocker (antagonist) of the test drug can be given to determine if the subjective effects are similarly blocked as previously studied effects.
(9)	Data are expressed as changes from the pre-drug (baseline) observations and are averaged across subjects. Depending on the temporal pattern, drug effects may be expressed either as peak effect or as the area under the time-action curve for changes in scores.

paranoia, andotheradverse effects, i.e., dysphoria (Haertzen 1966, 1974). Consistently, such drugs do not serve as effective reinforcers for animals (Griffiths et al., 1980). It is plausible that use of drugs in which there is a notable degree of both pleasant and unpleasant effects at typically ingested doses would be more dependent on nonpharmacologic factors than drugs which do not produce such striking dysphoric effects at commonly ingested doses.

Somewhat analogous to the findings with hallucinogens are those with caffeine. Caffeine is a drug that produces only weak elevations on the Liking and MBG scales while elevating scores on the LSD scale of the ARCI and also the Tension-Anxiety scale of the Profile of Mood States (Chait and Griffiths 1983). Consistent with such data are the observations that although caffeine is occasionally abused, the overwhelming majority of users do not use it in ways that are considered to be of significant adverse health effect (cf. Gilbert 1976; Greden 1981; Griffiths and Woodson 1988a,b). The subjective effects data suggesting limited potential of caffeine to cause abuse are also consistent with the findings that caffeine has not been shown to serve as an effective reinforcer for animals (Griffiths and Woodson, 1988b). Patterns of use and abuse of caffeine appear rather, to be heavily dependent upon social circumstance and pressure and perceived or actual beneficial effect. In addition, because caffeine exposure can produce physical dependence which is marked by undesirable withdrawal effects (including headaches, lethargy, and irritability), some use may occur as a means of avoiding such effects (Griffith and Woodson 1988a).

MAXIMIZING THE ACCURACY OF CONCLUSIONS

Accurate conclusions are a function of both the methods of empirical data collection as well as the analytic interpretation of data. To obtain valid and reliable data, it is important to follow the procedures for subjective effects assessment as summarized in table 2 and elsewhere (Jasinski 1977). In particular, use of appropriate positive and negative control substances as well as appropriate manipulations of drug dose, and the use of appropriate test subjects are fundamental. For example, variation in dose level should result in variation of response magnitude. Analogously, preloading subjects with antagonists should reduce the magnitude of responses (USDHHS 1988). Improvement of measurement techniques should also come with the innovative refinement of existing technology and the development of new technologies such as computerized testing and better observational techniques for verification of effects.

Improvement in accuracy can arise not only from careful use and appropriate modification of procedures for collecting data, but also from improved techniques of interpretation of data. Improvement via refinement of interpretation can be illustrated by examination of Single Dose Questionnaire data. The sensitivity of the instrument is greatest when data from only a single scale is used, namely can the subject "feel the drug." Such data are directly related to dose as determined according to double blind testing procedures, however, their specificity is poor. That is, no information is provided regarding the liking of the substance or the qualitative nature of its effects in comparison tootherdrugs. For example, such data do not allow discrimination between the rarely abused major tranquilizers and the widely abused psychomotor stimulants. Simply relying upon scales of the ARCI, on the other hand, may imply that low dose levels of addictive drugs are of little concern since they do not significantly elevate scale scores. When studied in combination, the scales which assess simple discriminability of drugs along with scales that provide qualitative information can provide accurate information about the potential of a certain drug to be abused and the dose threshold at which any relevant effects may occur.

Interestingly, analogous observations and refinement in methods of discrimination testing in animals were critical to establish animal drug discrimination testing as a viable means to assess abuse liability. Overton and his colleagues examined the hypothesis that simple determination of discriminative effects would be sufficient to assess abuse liability (Overton and Batta 1977). These researchers found that, although a sensitive, measure, simply determining that a drug could serve as a discriminative stimulus was not sufficiently specific for an abuse liability assessment; for example, opioids, stimulants, tricyclic antidressants, and antihistamines were approximately similar in their degree of discriminability (Overton and Batta 1977). By training animals to identify prototypic drugs of abuse and then determining the degree to which such identifications would generalize to the test drugs, a sensitive and specific procedure evolved (cf. Overton 1971; Goldberg et al., 1981b; Jarbe and Swedberg 1982; USDHHS 1988).

GENERALITY OF FINDINGS

The generality of data obtained from studies of subjective and physiologic drug effects has been widely confirmed by a number of lines of laboratory and nonlaboratory data. Patterns of drug use outside the laboratory frequently correspond to laboratory obtained subjective effects data. This

has been found both in analyses of subjective effects of drugs already known to be abused (e.g., morphine, cocaine, nicotine), as well as evaluation of drugs prior to their becoming widely available (e.g., pentazocine, nicotine polacrilex gum, buspirone) (Jasinski 1977; USDHHS 1988). Human subjective effects assessment data also are generally consistent with those obtained from animal and human abuse liability tests that utilize different test strategies. For example, two reviews reported strong correlations between animal drug self-administrationdata and human subjective effects data, i.e.. animals tended to self-administer drugs which produced morphine-like profiles of effects in humans (Griffiths and Balster 1979; Griffiths et al., 1980). Other kinds of laboratory data demonstrating mechanisms by which drugs can control behavior also correspond, to a rather remarkable degree, to data obtained from studies of subjective drug effects in humans. A summary of several such lines of data is provided in table 3. As shown in the table, there is a good general correspondence across data sources; however, each procedure and source of data provides additional information that is useful to fully characterize the potential mechanisms by which drugs can control behavior.

PRACTICAL APPLICATIONS OF SUBJECTIVE TESTING STRATEGIES

There are diverse practical and theoretical applications of subjective effects data. Studies of the subjective effects of drugs can provide basic data on the biologic basis of drug dependence itself, as well as serve to provide practical, useful information for drug development efforts. In these capacities, for example, such data led to the postulation of differing receptors to explain the diverse effects of opioids, they have helped to determine appropriate ligands for drug receptor studies, and to quantitate possible effects of therapeutic agents. These applications are not mutually exclusive and are often incorporated within single studies.

The application of subjective effects assessment as a practical means of abuse liability testing was not initially an end unto itself, but rather emerged as a product of basic studies of the biological basis of drug dependence. The usefulness of such data in making regulatory decisions about drugs, however, did lead to the emergence of abuse liability testing in its own right, largely in the 1960s and early 1970s. Although practically oriented, these studies continued to provide a substantial base of data upon which further theory related to the understanding and treatment of drug dependence rested. For example, a high degree of correlation was observed between drugs that were abused by humans, self-administered by animals,

Table 3. Characteristics of psychoactive drugs

Attribute	Nicotine	Cocaine	Morphine-like	Alcohol	Caffeine	Marijuana	Diethylamide	Chlorpromazine
Discriminable interoceptive (subjective) effects	+ Henningfield & Goldberg 1985; Morrison& Stephenson 1969	+ Fischman et al. 1976	+ Terry & Pellens 1970	+ Carpenter 1962	+ Gilbert 1976; Griffiths & Woodson 1988b	+ Siler et al. 1933	+ Hofmann 1975	+ Griffiths et al. 1979
Produce dose-related increases in self-reported "liking" scores	+ Henningfield, et al. 1985	+ Henningfield et al. 1987	+ Martin & Fraser 1961	+? Mello 1968	+- Griffiths, Bigelow, Liebson 1986; Chait & Griffiths 1983§; Griffiths & Woodson 1988b	+ Higgins & Stitzer 1986; Cone et al. 1986	?	?
Produce elevated response on MBG (euphoria) scale of ARC inventory	+ Henningfield, et al. 1985	+ Fischman et al. 1976	+ Haertzen et al. 1963	+ Henningfield et al. 1984; Stitzer et al. 1981	+- Chait & Griffiths 1983	- Higgins & Stitzer 1986; Cone et al. 1986	- Haertzen et al. 1963	- Stitzer et al. 1981
Positive reinforcer in animal drug self-administration studies	+ Goldberg et al. 1981a; Deneau & Inoki 1967; Ando & Yanagita 1981; Henningfield & Goldberg 1983a	+ Pickens & Thompson 1968; Deneau et al. 1969	+ Thompson & Schuster 1964	+ Deneau et al. 1969; Winger & Woods 1973	-? Deneau et al. 1969; Griffiths & Woodson 1988b	- Harris et al. 1974	- Hoffmeister & Wuttke 1976	- Hoffmeister & Goldberg 1973; Hoffmeister 1975; Deneau et al. 1969
Positive reinforcer in human drug self-administration studies	+ Henningfield, Miyasato, Jasinski 1983	+ Fischman & Schuster 1982	+ Jones & Prada 1975	+ Bigelow et al. 1975; de Wit et al. 1987	+? Griffiths et al. 1986; Griffiths, Bigelow & Liebson 1986; Griffiths & Woodson 1988b	+ Mendelson & Mello 1984	?	- Griffiths et al. 1979
Place conditioning	+ Fudala et al. 1985	+ Spyraki et al. 1982	+ Bardo &Neisewander 1986	+- Stewart & Grupp 1985	?	?	?	?
Physical dependence develops such that withdrawal accompanies abrupt abstinence	+ Hatsukami et al. 1984; Hughes & Hatsukami 1986	+? Carroll & Lac 1987; Jones 1984	+ Light & Torrance 1929a; Kolb & Himmelsbach 1938; Himmelsbach1941	+ Isbell et al. 1955	+ Griffiths, Bigelow, Liebson, 1986; Dreisbach & Pfeiffer 1943; Horst et al. 1934; Griffiths & Woodson 1988a	+? Jones & Benowitz 1976; Mendelson et al. 1984; Beardsley et al. 1986	- Isbell et al. 1956	- Baldessarini 1980
Tolerance develops	+ Langley 1905; Domino 1978; Marks et al. 1983 Jones et al. 1978	+ Tatum & Seevers 1929; Downs & Eddy 1932; Woolverton & Schuster 1977; Wood & Emmett-Oglesby 1987	+ Light & Torrance 1929b	+ Goldberg 1943	+ Carney 1982; Eddy & Downs 1928; Griffiths & Woodson 1988a	+ McMillan et al. 1970; Weil et al. 1968; Babor et al. 1975; Cone et al. 1986	+ Isbell et al. 1956	? Baldessarini 1980

Key: + = attribute was demonstrated; - = attribute was not demonstrated; ? = data are either unclear or unavailable. From U.S. DHHS 1988.

and produced key subjective effects of opioids and stimulants. These observations confirmed that the process of drug addiction involved basic biologic mechanisms which were common to diverse drugs and species (Crowley and Rhine 1985; Jasinski and Henningfield 1988; Jasinski 1988).

Perhaps the most practical application of subjective effects testing for abuse liability assessment is in the development of drugs with selective actions, i.e., retaining therapeutic efficacy with lowered abuse liability. New psychoactive drugs and formulations of psychoactive drugs are now routinely tested using such methods. For example, subjective effects data were important in evaluation of the serotonergic acting drugs, fenfluramine and buspirone, which were developed as anorectics and anxiolytics, respectively, with lower potentials for abuse than the prototypic substances that each was intended to replace (Griffith et al., 1975, 1986). Similarly, nicotine polacrilex gum was a new formulationof nicotine which subjective effects data had shown was low in abuse liability relative to several other forms of nicotine and other addictive drugs (Nemeth-Coslett et al., 1987; US DHHS 1988). Most recently, tilidine, transnasal butorphanol and picenadol were evaluated as selective drugs with low abuse liability for the treatment of pain, and zolpidem for the treatment of anxiety, using the methods described in this chapter (Jasinski et al., 1988; Jasinski and Preston 1986; Jasinski, personal communication).

As the aforementioned examples suggest, applications of this method include the evaluation of drugs whose chemical structure or intended therapeutic use differs from that of prototypic drugs used for assessments of pharmacologic equivalence. For example, new generations of behavioral performance enhancing drugs may be evaluated, and decisions rationally made, as to whether their profile of effects most resembles that of opioids, sedatives, stimulants, major tranquilizers, anticholinergics, or any other previously tested substances. Observations that a drug produces robust, dose-related elevations on the Liking and MBG scales are indices of a liability for abuse regardless of other characteristics.

The need for continued development of procedures for assessing subjective and physiologic drug effects is perhaps best illustrated by the continuing, although evolving problems of drug dependence and for public health needs for continued development of safer and more effective medications for the alleviation of disease and suffering. The facts that drugs, drug delivery systems, and public health needs continue to change imply that there will be a continuing need for practical and effective methods of abuse liability testing. The diversity of the challenges probably will require the continued maintenance of a diversity of methods of abuse liability assessment as represented in this volume and elsewhere (Goldberg

and Hoffmeister 1971; Thompson and Unna 1977; Brady and Lukas 1984; Bozarth 1987; USDHHS 1988).

As shown in this chapter, the strategy of abuse liability assessment relying upon subjective effects assessment in humans can be used to provide a quantitative and reliable base of data upon which rational decision making can be made. Procedural and interpretational strategies discussed in this chapter may strengthen the reliability, sensitivity and specificity of the data obtained. Further refinement of such methods and their incorporation into other strategies (e.g., combining human drug self-administration tests with subjective effects evaluations) should provide even greater reliability and specificity, and provide even more powerful tools for future challenges.

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ACKNOWLEDGMENTS

Table 3 is modified from one that was originally developed by R. J. Lamb and J.E. Henningfield for use in a report of the U.S. Surgeon General (USDHHS 1988).

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APPENDIX A

Items of single-dose opiate questionnaires (from Jasinski 1977).

Subject rating	Observer rating
1. Do you feel the medicine? Yes No	Any evidence of drug effect? Yes No
2. Drug is most like what drug listed below (check 1):	Behavior is like that seen after:
a) Blank	a) Blank
b) "Dope" (opiate or potent analgesics)	b) "Dope" (opiate or potent analgesics)
c) Cocaine	c) Cocaine
d) Marijuana (pot)	d) Marijuana (pot)
e) Barbiturate ("goofballs")	e) Barbiturate ("goofballs")
f) Alcohol*	f) Alcohol*
g) Benzedrine (amphetamine, speed, bennies. methedrine)	g) Benzedrine (amphetamine, speed, bennines, methedrine)
h) LSD (acid)*	h) LSD (acid)*
i) Thorazine*	i) Thorazine*
j) Miltown or Librium*	j) Miltown or Librium*
k) Other	k) Other
3. Check each of the sensations you feel:	Check each item which you think the patient shows:
a) Normal (no change)	a) Normal
b) Turning of stomach (1)	b) Scratching (2)
c) Skin itchy (2)	c) Red eyes (1)
d) Relaxed (1)	d) Relaxed (1)
e) "Coasting" (2)	e) "Coasting" (2)
f) "Soapbox" (1)	f) "Soapbox" (1)
g) Pleasant sick (1)	g) vomiting (1)
h) Drive (2)	h) Nodding (2)
i) Sleepy (2)	i) Sleepy (1)
j) Nervous (1)	j) Nervous (1)
k) Drunken (1)	k) Drunken (1)
1) Other	1) Other
4. My liking for this drug is most nearly described by which of the following:	How much do you think patient liked the effects of this drug?
a) Not at all (0)	a) Not at all (0)
b) Slight (1)	b) Slight (1)
c) Moderate (2)	c) Moderate (2)
d) A lot (3)	d) A lot (3)
e) An awful lot (4)	e) An awful lot (4)
f) Other	f) Other

( ) The figures given following items of questions 3 and 4 are the weights given to the particular responses for the purpose of calculating the opiate symptom, opiate sign, subject's "liking" and observer's "1iking"scores (Martin and Fraser 1961).

* Items were not in the original single-dose opiate questionnaire.

APPENDIX B

The forty items from the Addiction Research Center Inventory utilized in multiple-scale questionnaires to distinguish the subjective effects of nalorphine andcyclazocine from those of morphine (from Jasinski 1977).

Morphine-Benzedrine Group WBG)	Pentobarbital-Chlorpromazine-Alcohol Group(PCAG)	LSD-Specific
I would be happy all the time if I felt as I do now.	*My speech is slurred.	*I have a weird feeling.
I feel as if I would be more popular with people today.	I am not as active as usual	I have a disturbance in my stomach.
Today I say things in the easiest possible way.	I have a feeling of just dragging along rather than coasting.	I feel an increasing awareness of bodily sensation.
*I feel more clear-headed than dreamy.	*I feel more clear-headed than dreamy (answered negatively).	I would be happy all the time if I felt as I do now (answer in negatively).
Things around me seem more pleasing than usual.	I feel sluggish.	I feel anxious and upset.
I have a pleasant feeling in my stomach.	*A thrill has gone through me one or more times since I started the test (answered negatively).	*A thrill has gone through me one or more times since I started the test.
I feel a very pleasant emptiness.	My head feels heavy.	My movements are free, relaxed and pleasurable (answered negatively).
I fear that I will lose the contentment I now have.	I feel like avoiding people although I usually do not feel this way.	I feel very patient (answer negatively).
I feel in complete harmony with the world and those about me.	I feel dizzy.	I have unusual weakness of my muscles.
I feel less discouraged than usual.	*I am full of energy (answered negatively).	Some parts of my body are tingling.
I can completely appreciate what others are saying when I am in this mood.	People might say that I am a little dull today.	It seems I'm spending longer than I should on each of these questions.
I would be happy all the time if I felt as I feel now.	It seems harder than usual to move around.	My hands feel clumsy.
I am full of energy.	I am moody.	I notice my hand shakes when I try to write.
Iaminthemoodtotalk about the feeling I have.	*I feel drowsy.	* I feel drowsy (answered negatively).
I feel so good that I know other people can tell it.	I feel more excited than dreamy (answered negatively).	
I feel as if something pleasant had just happened to me.		

* contained in more than one scale but scored for the appropriate scale depending upon the positive or negative answers.

CHAPTER 6

Drug Discrimination: Methods for Drug Characterization and Classification

George E. Bigelow, Ph.D.
Kenrie L. Preston, Ph.D.

INTRODUCTION

The prototypic method for assessing the abuse liability of novel drugs is to assess the extent to which their effects are similar to the effects of known drugs. Test drugs are compared to reference drugs of known abuse liability, and drugs with similar effects are considered likely to have similar abuse liabilities. This approach, of comparing the test drug to a known reference drug, is the methodology developed and used for several decades by the USPHS Addiction Research Center. One of the useful elements of that methodology has been a question asking subjects to identify the pharmacological class to which test drugs are most similar — i.e., is the test drug morphine-like, barbiturate-like, amphetamine-like, etc? One limitation of this question is that it relies upon subjects' uncontrolled and variable prior experience with the various drug classes. The approach to be discussed here - the use of a behavioral drug discrimination methodology - avoids this problem by providing explicit, standardized training experience with each of the reference drugs prior to asking subjects to evaluate the similarity of test drugs to those reference standards.

In human subjects the drug discrimination methodology provides a unique opportunity to assess the similarity of test compounds to reference compounds in multiple dimensions and, thereby, to assess the comparability of drug characterization and classification decisions suggested by different measures. The results of drug discrimination testing can be compared with the results of assessing the profile of acute effects on other subjective, behavioral and physiological indices; these other measures can be conveniently collected concurrent with drug discrimination training and testing. Perhaps the most interesting of these

concurrently-available data are measures of the subjective effects produced by the drugs. Subjective effects appear to be related to abuse potential, and their measurement has constituted a significant element of traditional abuse liability testing in humans (Jasinski 1977). The discriminative stimulus effects of drugs have been considered analogous to their subjective effects (Holtzman 1985). Human drug discrimination studies provide a unique opportunity to assess this relationship.

DRUG DISCRIMINATION PROCEDURES

The methodology for drug discrimination testing is derived from the animal laboratory, where it has become one of the mostly widely used paradigms in behavioral pharmacology (Stolerman and Shine 1985; Stolerman et al., 1982). Investigators face the problemof asking subjects without prior drug experience to assess the similarity of test drugs to other, known drugs; and, of course, the added problem that in the animal laboratory this similarity-assessment question is asked of nonverbal subjects. Therefore, two elements have been necessary for investigators to obtain this assessment — first, providing the experience of pharmacological exposure to the reference drugs against which similarity is to be judged; and second, training a behavioral response that allows the subject to indicate the degree of similarity of test drugs to the reference drugs. The behavioral procedure used has involved operant conditioning procedures (i.e., response contingent reinforcement) to train subjects to emit different responses in the presence of different drug conditions. One of the reference, or training drugs, is administered shortly prior to each experimental session, and is considered to act as a drug stimulus. For each training drug stimulus there is a specific response that will lead to reinforcement; other responses are unreinforced. Two or three training drugs are administered in a mixed order across sessions so that subjects can learn to make the correct response in the presence of each training drug stimulus. As with traditional sensory discriminations subjects rapidly learn correct discriminative performance (Overton 1984).

The behavioral procedure for drug discrimination training is presented schematically in figure 1. Most drug discrimination studies are conducted with only two alternatives — typically one active drug versus placebo. Figure 1, however, illustrates the procedure for a more complex three-choice discrimination.

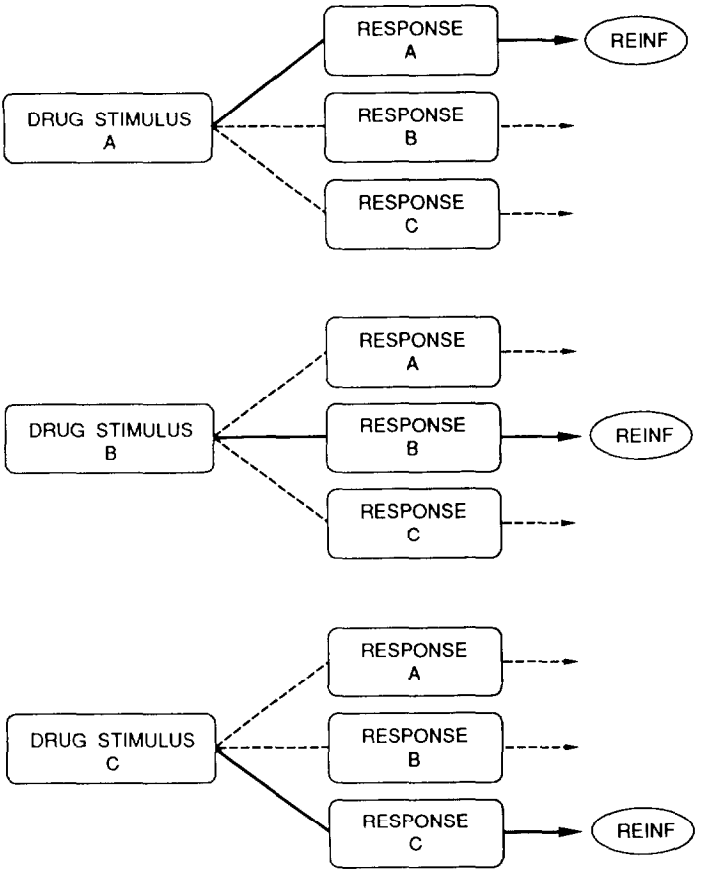

Figure 1: *Schematic representation of the behavioral contingencies used in training and maintaining a three-choice drug discrimination performance. Each drug stimulus is associated with a distinctive response which, if made following the appropriate drug treatment, leads to reinforcement (monetary payment in the case of the present studies with human volunteers); incorrect responses are unreinforced.*

OPIOID DRUG DISCRIMINATION

The discriminative stimulus properties of opioid drugs have been extensively studied in the animal laboratory (Holtzman 1983). To illustrate the use and value of drug discrimination methods in humans, we will rely primarily upon our own work concerning discrimination of opioid agonists,

antagonists, and mixed agonist-antagonists with opioid-experienced post-addict volunteers. Detailed descriptions of these methods are provided elsewhere (Preston et al., 1987; Bickel et al., in press; Preston and Bigelow, in press); the emphasis here will be on the unique contributions that the drug discrimination methodology can make to the task of characterizing and categorizing the nature of opioid drug effects and to assessing their likely abuse liability. The studies are conducted in a residential laboratory setting where the volunteer participants remain throughout the experiments.

Method

These studies have generally utilized a three-drug discrimination procedure as illustrated in figure 1. In this procedure, recognition of and differential responding to each of three different pharmacological stimuli is trained. The drug stimulus conditions have included saline placebo plus two different active opioids. The active opioid training drugs have been chosen to represent opioids acting via different opioid receptor mechanisms. Hydromorphone has been used as the prototypic morphine-like mu-receptor agonist. Pentazocine has been used as the prototypic kappa-receptor agonist. Specifically, in the work to be described below, a discrimination has been trained between intramuscularly administered saline, hydromorphone HCl 3 mg, and pentazocine lactate 45 mg.

Studies have proceeded in three phases: training, test of acquisition, and testing. Sessions of 1-2 hour duration are scheduled daily, and subjects remain in a residential laboratory setting throughout the approximately 8 week study duration. Subjects are paid for their research participation, and the amount of their payment is contingent upon their accurately discriminating the training drugs; all earnings are paid after completion of the study. Subjects are told at the study outset that their task is to attend carefully to the drug effects and to try to learn to discriminate among drugs, which are identified only by arbitrary letter codes — e.g., A, B, C.

In the training phase subjects receive, in a random order, two sessions of exposure to each of the three training drugs; at the start of each of these sessions subjects are informed of the letter code of the drug they are receiving and then respond to that letter code during the session.

During the subsequent test of acquisition phase, subjects again receive, in randomorder, two sessions of exposure to each of the three training drugs with no prior information provided; in these sessions subjects' earnings are contingent upon their accurate identification of the drugs by letter code. At the end of each session a codeenvelope is opened which identifies

the administered drug by letter code, thus providing confirmation of the subject's discrimination response as well as indicating the amount of money earned. This procedure provides a test of the accuracy of the acquired discrimination as well as continued training.

Following acquisition of the discrimination, subjects enter the test phase during which novel drugs or novel doses of the training drugs are administered to assess their similarity to the three training drug conditions. Further test of acquisition sessions with the training drugs/doses are interspersed during this phase to provide continued training and contingent reinforcement for correct drug discrimination performance. In trials with novel test conditions there is no "correct" response, so at the session conclusion subjects are informed this was a test trial and the drug identity can not be revealed; they are paid in proportion to the accuracy of their discrimination on the most recent test of acquisition trials.

Discrimination Performance

That this opioid drug discrimination is rapidly and accurately learned by human volunteers is illustrated in figure 2, which shows the average drug discrimination performance during the six-session test of acquisition phase for six nondependent opioid post-addict subjects. After only two prior training exposures to each of the drug conditions, both saline and hydromorphone were correctly discriminated 100 percent of the time. Pentazocine showed some stimulus overlap with hydromorphone but was correctly discriminated 75 percent of the time.

Relation to Subjective Indices

One of the great strengths of the drug discrimination procedure in humans is that it permits the concurrent assessment of a wide range of subjective and objective indices of acute drug effects that are themselves commonly used in assessing the likely abuse potential of drugs. One of the commonly used subjective effect questions in such assessments, and acomponent of the Single Dose Questionnaire (SDQ) developed by the USPHS Addiction Research Center for opioid abuse liability assessments (Jasinski 1977), is drug class identification. In this procedure subjects are simply asked what drug class they think they have received — e.g., opiate, barbiturate, CNS stimulant, etc. On its surface it might appear that the drug discrimination procedure is simply a complicated way of asking this question. Therefore, it is important to emphasize that the drug discrimination procedure is not functionally identical to such verbal subjective-identification questions; it can yield drug characterizations and categorizations that differ from those provided by verbal techniques.

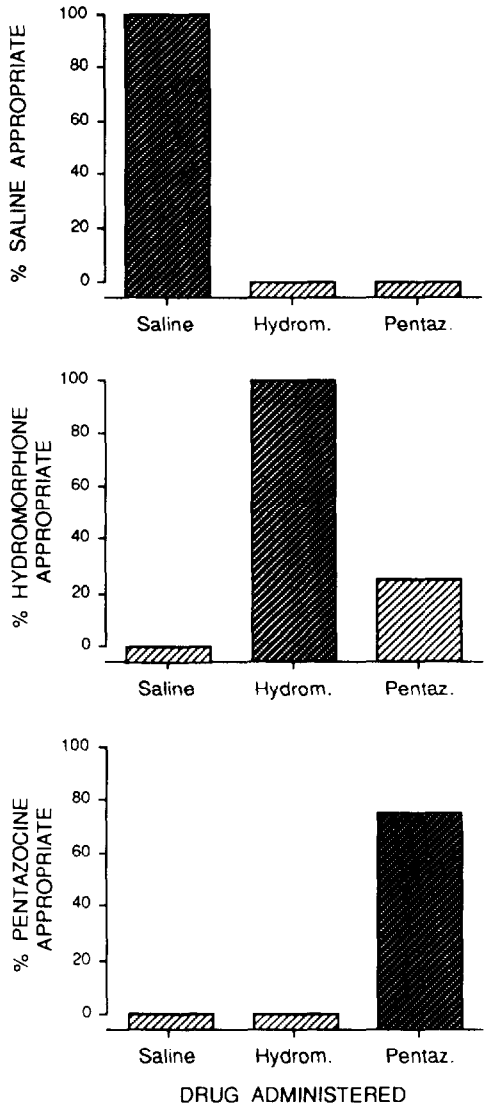

Figure 2: *Distribution of drug discrimination responding by nondependent human opioidpost-addicts to the three training drug conditionsduring the test-of-acquisition phase. Each column shows the mean percent of responding allocated to each of the three response alternatives. In each panel the correct response category is darkened. The drug conditions were saline, hydromorphone 3 mg, and pentazocine 45 mg, given intramuscularly.*

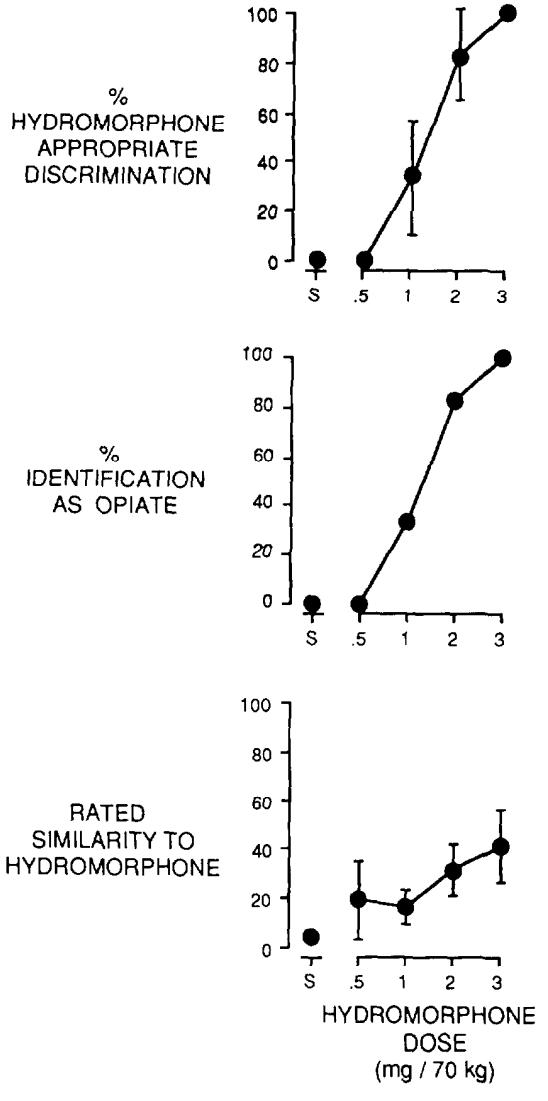

Figure 3: *Comparison of behavioral drug discrimination performance (top panel) with two subjective effect indices — categorical identification as an opiate on a drug identification questionnaire (middle panel), and rated similarity to the training dose of 3 mg hydromorphone on a 100-point visual analog scale (bottom panel). Saline (S) and a range of hydromorphone doses were tested.*

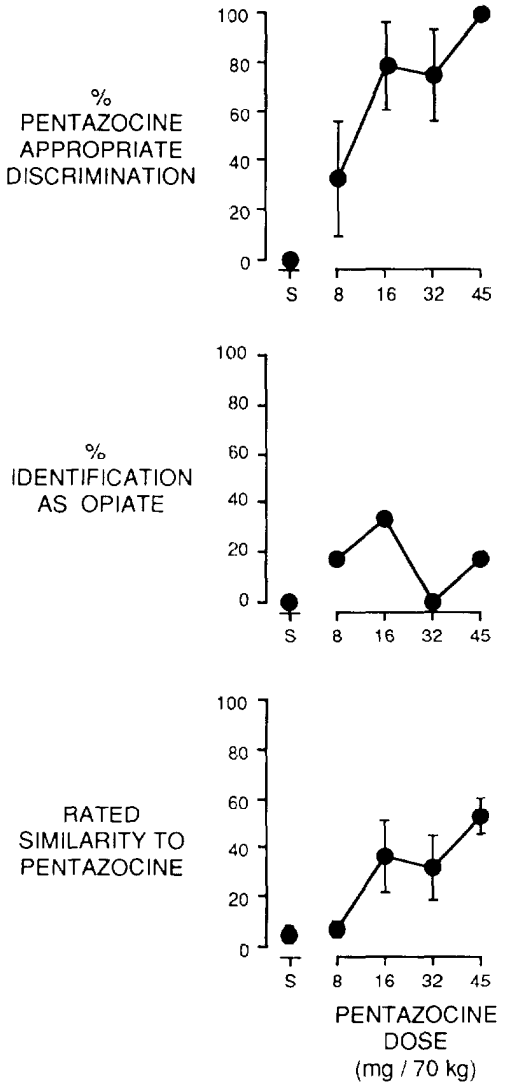

Figure 4: *Comparison of behavioral drug discrimination performance (top panel) with two subjective effect indices — categorical identification as an opiate on a drug identification questionnaire (middle panel), and rated similarity to the training dose of 45 mg pentazocine on a 100-point visual analog scale (bottom panel). Saline (S) and a range of pentazocine doses were rested.*

pentazocine, respectively, the dose-response relation for three different types of drug identification procedures. These data were collected during test phase exposure to a range of doses of the the two active training drugs.

The top panel in each figure shows the trained and reinforced drug discrimination performance; in both cases as the dose of the test drug increased it was discriminated as being more similar to the training drug, with test doses equal to the training dose being correctly discriminated 100 percent of the time. The other two panels in each figure show the results from two different verbal-categorization responses, neither of which had received explicit training and reinforcement.

The center panel in each figure shows the percent of identifications as an opiate on a drug class identification questionnaire. For hydromorphone there is good correspondence between behavioral drug discrimination performance and subjective drug class identification, but this is not true for pentazocine. Pentazocine is accurately discriminated in a dose-related fashion as pentazocine-like, but it is not systematically identified as an opiate.

The bottom panel in each figure shows the subjective rating on a 100-point visual analog scale of the similarity of the test dose to the training drug (identified by letter code); e.g., “how much is it like Drug A?”. For neither hydromorphone nor pentazocinedoes this nonreinforced subjective assessment of similarity bear a close correspondence to the trained and reinforced behavioral discrimination performance.

Assessment of Novel Test Conditions

The purpose of training the 3-way opioid drug discrimination that we have been discussing was to utilize it to assess the profiles of action of a variety of opioid mixed agonist/antagonists. It is our belief that the drug discrimination procedure can make especially unique contributions to the task of characterizing and categorizing drugs with complex and overlapping profiles of action. This is a task that can be quite difficult when based upon examination of acute drug effects on a wide range of subjective and objective indices, i.e., the traditional method of assessing the similarity of the acute profiles of effects.

To illustrate the value of the drug discrimination procedure it may be useful to begin by illustrating the difficulty one can face in making decisions about the similarities and differences among drugs based upon examining the profiles of their acute effects. The data we present here are based upon test phase assessments of a range of doses of the two active training drugs

(hydromorphone and pentazocine) as well as three marketed opioid mixed agonist/antagonists — butorphanol, nalbuphine, and buprenorphine.

All five of these drugs produced statistically significant dose-related pupillary constriction (data not shown), as is characteristic of opioid analgesics. However, their profiles of subjective effects differed considerably. Their profiles of action over a range of doses on three different subjective effect measures are shown in figure 5.

The left hand column of figure 5 presents the dose-effect functions for responses on an adjective rating scale questionnaire designed to detect typical morphine-like opioid agonist subjective effects. Only hydromorphone produced statistically significant effects on this variable, but butorphanol achieved borderline significance ($p=0.067$), suggesting that, of these five drugs, hydromorphone and butorphanol are most similar to one another on this dimension.

The center column of figure 5 presents the dose-effect functions for responses on a 100-point visual analog scale rating of subjective liking of the drug effect. Both hydromorphone and pentazocine produced statistically significant effects on this variable, and buprenorphine achieved borderline significance ($p=0.053$), suggesting that, of these five drugs, hydromorphone, pentazocine, and buprenorphine are most similar to one another on this dimension.

The right hand column of figure 5 presents the dose-effect functions for responses on the Lysergic Acid Diethylamide (LSD), or "dysphoria," scale of the Addiction Research Center Inventory (ARCI). Pentazocine, butorphanol, and buprenorphine each produced statistically significant effects on this variable, suggesting that, of these five drugs, these three are most similar to one another.

The point to be made from the above data is that examination of the acute profile of effects of test drugs on multiple variables can result in confusing and contradictory patterns of similarities and differences. While this method is extremely valuable in assessing and comparing drug effects, it is by no means a simple method for reaching conclusions about the characterization and categorization of test drugs.

Nor does the method of asking subjects to identify the drug class they received always provide an accurate characterization or categorization of the test compound. Test drugs may be identified as belonging to incorrect pharmacological classes. Table 1 summarizes subjects' answers to a pharmacological class questionnaire administered during the test phase

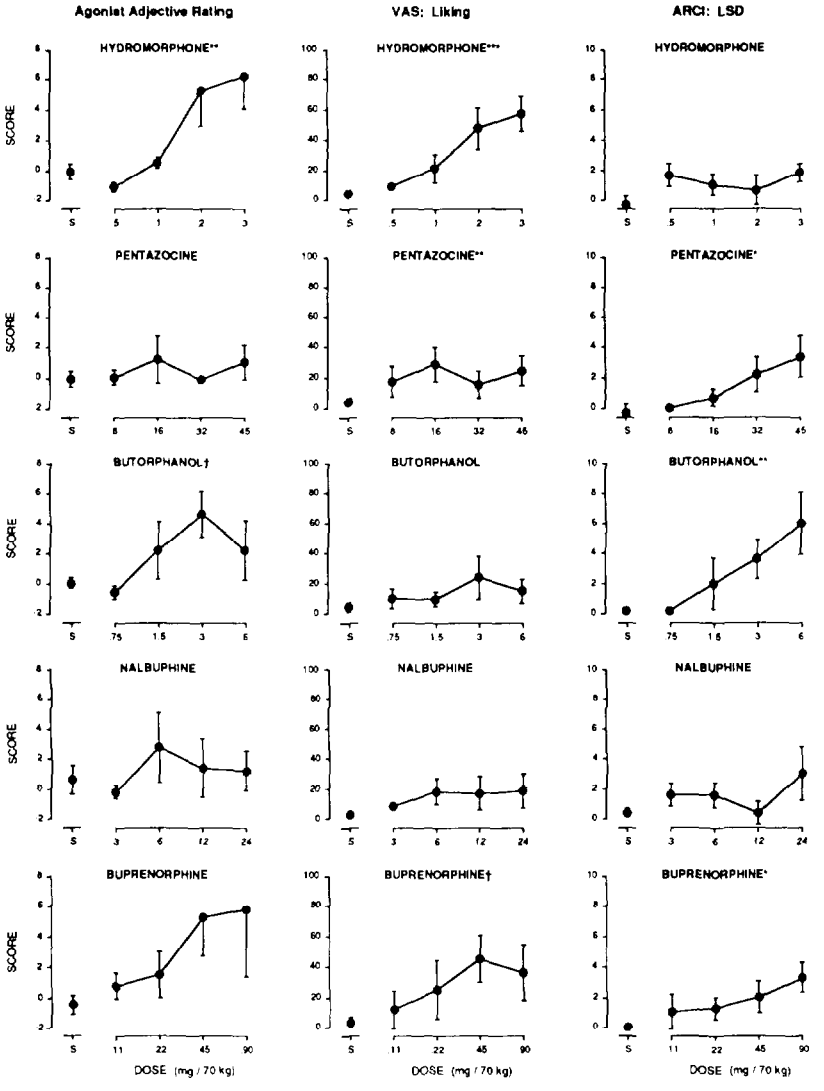

Figure 5: *Profile of subjective effects for five opioid analgesics assessed over a range of doses during a drug discrimination study in nondependent human opioid post-addicts. † p<0.10; * p<0.05; ** p<0.01; *** p<0.001*

pharmacological class questionnaire administered during the test phase of our assessment of a range of doses of hydromorphone, pentazocine, butorphanol, nalbuphine, and buprenorphine. The pharmacological class questionnaire responses are collapsed across all test drugs and doses but are summarized separately according to the subjects' behavioral drug discrimination response. As can be seen, whenever a test drug condition was discriminated as being either saline-like or hydromorphone-like the drug class questionnaire response tended to show good agreement with the discrimination performance. Drug classes were labeled as 97 percent "blank" and 76 percent "opiate" when discriminated as being saline-like or hydromorphone-like, respectively. However, there was no agreeement between the pharmacological class questionnaire response and the drug discrimination response when the test condition was discriminated as being pentazocine-like. Pharmacological class identifications covered quite a broad range, with Benzodiazepine being the most common identification, but also with substantial identifications as Stimulant, Hallucinogen, or Opiate Antagonist; test conditions discriminated as pentazocine-like were only rarely identified as Opiate.

Table 1. Relationship between behavioral drug discrimination and subjective drug class identification

	Behavioral Discrimination[1]		
Subjective Drug Class Identification	Saline-Like N=78	Hydromorphone-Like N=71	Pentazocine-Like N=111
Blank	97	1	2
Opiate	3	76	3
Benzodiazepine	-	18	27
Barbiturate	-	4	7
Stimulant	-	-	22
Hallucinogen	-	-	18
Antidepressant	-	-	5
Opiate Antagonist	-	-	17

[1] Entries are percents of each column; columns may not total to 100 due to rounding. For clarity 0 percent entries are not shown.

The results for the behavioral drug discrimination performance for the five test drugs (collected in the same sessions as the above acute effect data) are presented in figure 6. The left hand column shows the extent of saline-appropriate responding as a function of dose; all five drugs are discriminated as being significantly not saline-like. The center column shows the extent of hydromorphone-appropriate responding as a function of dose. Only hydromorphone is discriminated as being significantly hydromorphone-like; both nalbuphine and buprenorphine show partial, but statistically nonsignificant, generalization to the hydromorphone stimulus. The right hand column shows the extent of pentazocine-appropriate responding as a function of dose. Both pentazocine and butorphanol show statistically significant complete generalization to the pentazocine training stimulus. Bothnalbuphine and buprenorphine show partial generalization to the pentazocine stimulus; in the case of nalbuphine this reaches borderline statistical significance ($p=0.058$).

Conclusions

Thus, these behavioral drug discrimination results lead us to conclude that none of the tested mixed agonist/antagonists is completely hydromorphone-like, and that only butorphanol completely shares the stimulus properties of pentazocine. Nalbuphine and buprenorphine are both judged as having stimulus properties that partially overlap those of both hydromorphone and pentazocine.

Animal laboratory drug discrimination studies indicate that opioids' stimulus properties appear to be related to their profile of opioid receptor activity. Therefore, our above drug discrimination data, in combination with data from subsequent studies examining other trained opioid discriminations, as well as data from other sources have led us at present to conceptualize the actions of these various opioids as follows: hydromorphone appears to be a pure mu-receptor agonist; butorphanol appears to be a kappa-receptor agonist and a mu-receptor antagonist; buprenorphine appears to be a mu-receptor partial agonist; pentazocine and nalbuphine appear to be mu-receptor partial agonists and kappa receptor agonists. This conceptualization remains open to modification on the basis of additional data, and it may well be true that the mu-receptor/kappa-receptor model of opioid activity is insufficient to account for the complexity of opioid drug actions. However, the primary point to be made here is the procedural one, that the drug discrimination methodology in humans can serve as a valuable complement and adjunct to other procedures for characterizing and categorizing drugs, especially drugs with complex and overlapping profiles of activity.

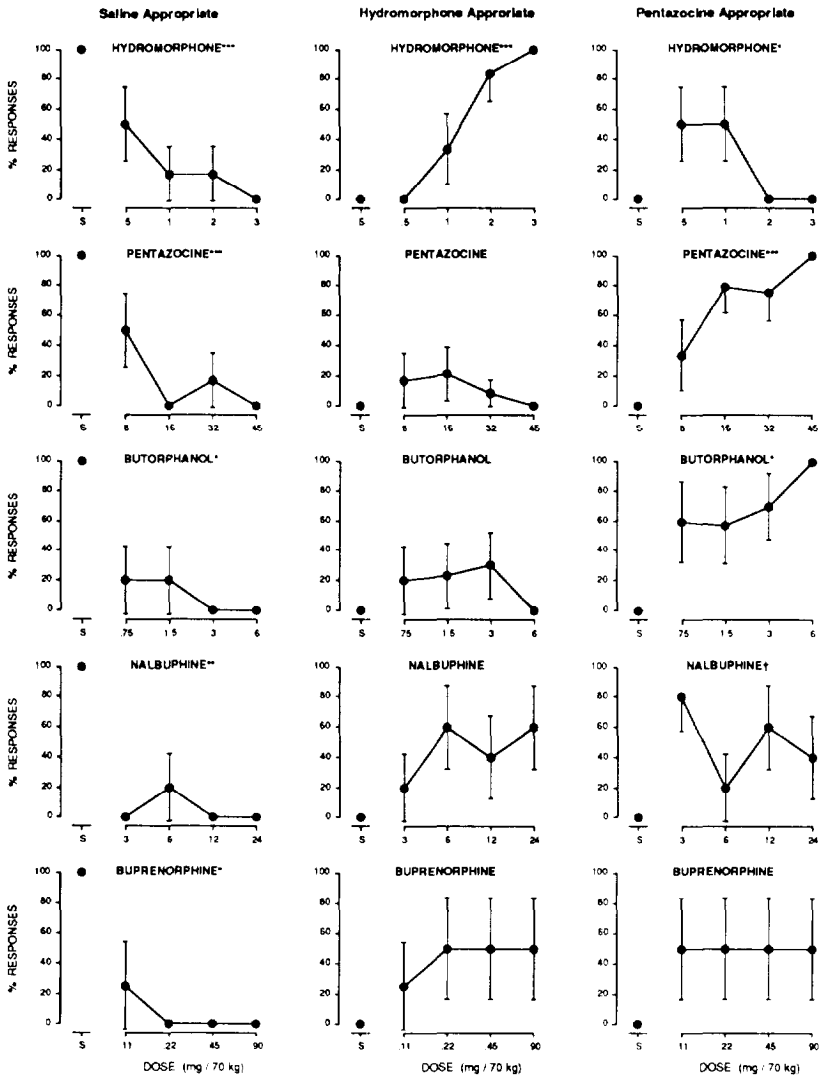

Figure 6: *Profile of behavioral drug discrimination responding for five opioid analgesics assessed over a range of doses in nondependent human opioid post-addicts. † p<0.10; * p<0.05 ** p<0.01; *** p<0.001*

OTHER DRUG DISCRIMINATIONS

While we have used our opioid discrimination studies as the vehicle for discussing drug discrimination methods, application of the methods is by no means limited to the opioids; rather, the methods can be extended to a broad range of pharmacological classes. At this time we do not know the full breadth of drug classes for which drug discriminations can be established in humans, simply because the efforts have not yet been made. Data from the animal laboratory certainly indicate that drug discriminations can be established with a very broad range of drug types, probably including all of the drugs of abuse. The expectation is that the same will be true for humans.

Besides opioid drug discriminations human studies so far have documented the establishment of drug discriminations for nicotine delivered in tobacco smoke (Kallman et al., 1982), for Δ^9-THC delivered in marijuana smoke (Chait et al., 1988), for caffeine delivered orally (Griffiths and Evans, personal communication), and for *d*-amphetamine delivered orally (Chait et al., 1986a).

Kallman et al., (1982) trained regular tobacco cigarette smokers to discriminate between two cigarettes which differed only in their nicotine yields. The smokers were one-hour abstinent from tobacco at the time of training and smoked complete cigarettes in their normal fashion. Subjects received single sampling exposures to each cigarette (identified by letter code) prior to the start of discrimination testing. The ease of learning the discrimination was directly related to the difference in nicotine yields of the two cigarettes. The discrimination between the two moderate-yield cigarettes (0.28 vs 0.69 mg nicotine) was not well learned, being mastered by only 27 percent of subjects. In contrast, the discrimination between the high-yield and low-yield cigarettes (1.30 vs 0.14 mg nicotine) was readily learned, being mastered by 94 percent of subjects; in addition, this discrimination was rapidly learned, apparently being immediately established with only the single training exposures to each cigarette. These results further document the speed with which humans can learn drug discriminations.

Chait et al., (1988) trained experienced marijuana users to discriminate between the effects of smoked marijuana (4 puffs) containing 2.7 percent Δ^9-THC versus 0 percent Δ^9 THC and then tested with two lower doses (concentrations) of marijuana cigarette. All subjects learned the discrimination. Test conditions with 0.9 percent and 1.4 percent Δ^9-THC marijuana cigarettes resulted, respectively, in 20 percent and 100 percent

marijuana-appropriate responses. Thus, the drug discrimination behavior was appropriately dose-related, with the 1.4 percent dose completely generalizing to the 2.7 percent training condition, and the 0.9 percent dose failing to generalize and being discriminated as predominantly placebo-like. These data further document the dose-related generalization of drug stimulus effects to the training drug conditions.

In as yet unpublished work in our laboratory Griffiths and Evans (personal communication) have established discriminations between orally administered caffeine versus placebo in humans. Participants are normal volunteers; they are experienced caffeine users (in the sense of their being usually exposed to caffeine in the normal dietary range), but they maintain a caffeine-free diet during the drug discrimination study. Discrimination of 100 mg of caffeine versus placebo has been established in 100 percent of participants. Since this dose falls within the normal dietary range for caffeine, these results serve to emphasize the subtlety of drug effects for which effective behavioral discriminations can be established.

The most comprehensive series of human drug discrimination studies yet published is that of Chait and colleagues concerning discrimination of orally administered d-amphetamine 10 mg versus placebo. A description of their methodology is provided by Chait et al., (1984). Participants in these studies have been normal volunteers without histories of drug abuse. Sessions occurred 3 days per week. Subjects received single sampling exposures to each of the training drugs (identified only by letter code) and then, over the next six sessions, were asked to discriminate which one they had received that day. Volunteers participated on an ambulatory basis, in which they reported to the laboratory in the morning to receive a study drug and then went about their normal daily activities. They filled out subjective effect questionnaires at 1, 3, and 6 hours following drug administration and, at hour 6, telephoned the experimenter to provide their drug discrimination response (i.e., identifying the study drug by letter code). Those who correctly learned the discrimination progressed on to a test phase in which they were tested with novel drugs and/or with novel doses of the training drug.

Three studies have been reported in this series; one (Chait et al., 1985) tested a range of d-amphetamine doses (2.5,5, and 10 mg) and a single dose of diazepam (10mg); another (Chait et al., 1986a) tested the anorectics phenmetrazine (25 and 50 mg) and fenfluramine (20 and 40 mg); and the other (Chait et al., 1986b) tested the anorectics phenylpropanolamine (25 and 75 mg) and mazindol (0.5 and 2 mg). Results of all three studies are summarized in figure 7 (from Chait et al., 1986c), which shows the percent *d*-amphetamine-appropriate discrimination responses during the test phase

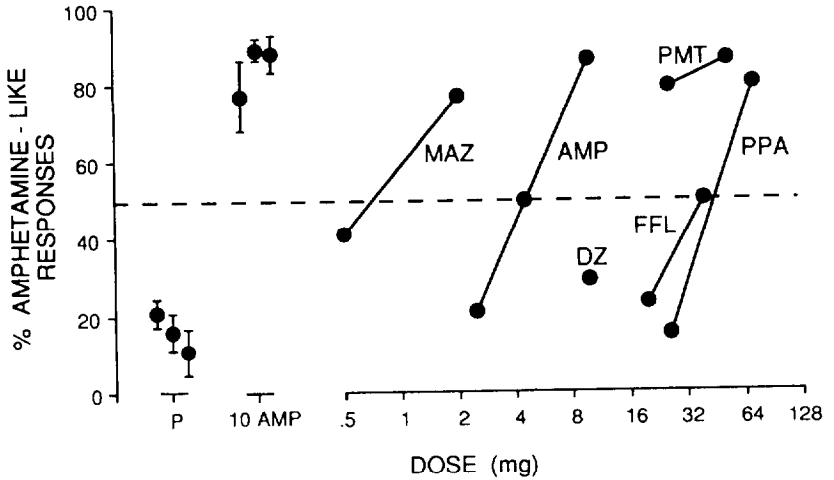

Figure 7: *Percent of amphetamine-like discrimination responses by normal human volunteers trained to discriminate between placebo (P) and 10 mg d-amphetamine p.o. (10 AMP) is shown for the two training drugs and for a range of test drugs - primarily anorectics. MAZ, mazindol; AMP, d-amphetamine; DZ, diazepam; FFL, fenfluramine; PMT, phenmetrazine; PPA, phenylpropanolamine. The data summarize three experiments and are redrawn from Chait et al., (l986c).*

d-amphetamine-appropriate discrimination responses during the test phase for the training conditions and each of the test conditions. The dashed horizontal line at 50 percent in the figure represents the "chance" level in this 2-choice procedure. The discrimination between 10 mg *d*-amphetamine and placebo was well-maintained throughout the test phase, averaging better than 80 percent correct. All of the anorectics, except fenfluramine, generalized to the d-amphetamine stimulus (>75 percent amphetamine-appropriate responses), at least at their highest dose. Neither fenfluramine nor 10 mg diazepam generalized to the d-amphetamine stimulus.

These data from the studies of anorectic drugs by Chait and co-workers raise questions concerning the utility of human drug discrimination procedures for the assessment of abuse liability. In these studies the higher doses of both mazindol and phenylpropanolamine were discriminated as being *d*-amphetamine-like; but neither of these drugs appears in other contexts to possess amphetamine-like abuse liability or to produce amphetamine-like subjective effects. Therefore, we discuss below several factors that may be relevant to using drug discrimination procedures in efforts to assess abuse potential.

RELATION TO ABUSE LIABILITY ASSESSMENT

First, it must be emphasized that drug discrimination procedures assess the stimulus properties of drugs, not their reinforcing properties. These are not necessarily the same thing; drugs with similar stimulus properties may have differing reinforcing effects, just as drugs with differing stimulus properties may have similar reinforcing effects. Thus, the aspect of the drug stimulus complex that individuals use to learn a drug discrimination is not necessarily the same as the aspect(s) of drug effects related to abuse liability.

Second, it may be that studies intending to assess the dimension of abuse liability should use as subjects individuals with personal histories of drug abuse rather then relatively drug-naive non-abusers. The majority of data documenting the ability of clinical testing to predict abuse liability has been developed with subjects with extensive drug abuse histories (Jasinski 1977). However, in the Chait et al., anorectic studies discussed above, in which the non-abused drugs mazindol and phenylpropanolamine were discriminated as being amphetamine-like, the subject participants were specifically selected for absence of a history of drug abuse. While assessment of drug effects in normal, non-drug-abuser populations is scientifically very interesting, its relevance to the assessment of abuse liability remains uncertain at this time. It is possible that drugs may have different stimulus properties in abusers versus non-abusers, or that discrimination behavior might come under control of different aspects of the drug stimulus complex in the two different populations. One certainly wonders whether experienced stimulant abusers would also discriminate mazindol and phenylpropanolamine as being amphetamine-like. This issue of the utility of non-drug-abuser populations for assessing abuse liability and of the comparability of abuser and nonabuser populations is fascinating and deserves considerably more investigation. However, at this time we would recommend that studies intended to assess drug abuse liability in humans should select as subjects volunteers with histories of drug abuse.

Third, drug discrimination behavior may have greater pharmacological specificity if it is trained in a procedure with more than two alternatives. Animal laboratory drug discrimination studies indicate that an increased number of training and response alternatives tends to sharpen the specificity of the discrimination (Overton 1984). A two-choice procedure does not permit as refined a distinction among drugs as would a procedure with more training drugs and more discriminative response alternatives. Theoretically, a two-choice drug versus placebo discrimination procedure

could result in a drug-no drug discrimination performance with minimal specificity. The important impact of the number and type of training drug alternatives is illustrated in table 2, which summarizes human drug discrimination performance with a group of opioid agonists and mixed agonist/antagonists studied under two different training conditions. The right hand column shows the percent of hydromorphone-appropriate discrimination responding in the three-choice discrimination study described earlier, in which subjects were trained to discriminate among hydromorphone, pentazocine, and saline (Preston et al., in press). In this procedure only hydromorphone was consistently discriminated as being hydromorphone-like; none of the mixed agonist/antagonists generalized completely to the hydromorphone stimulus. In contrast, the left hand column shows the percent of hydromorphone-appropriate discrimination responding in a two-choice discrimination study in which subjects were trained to discriminate between hydromorphone and saline (Preston and Bigelow unpublished data). In this two-choice procedure, all of the mixed agonist/antagonists were discriminated as being hydromorphone-like. Thus, the number and/or nature of the training drug alternatives can clearly have a dramatic influence upon how test drugs are characterized or categorized in a drug discrimination assessment. It seems that more

Table 2. Influence of discriminative response alternatives upon opioid discrimination behavior

	Mean Percent Hydromorphone-Appropriate Responding	
Drug[1]	2-Choice Procedure[2]	3-Choice Procedure[3]
Hydromorphone 3 mg	100	100
Pentazocine 45 mg	80	0
Butorphanol 6 mg	100	0
Nalbuphine 24 mg	100	60
Buprenorphine 0.9 mg	100	50

[1] All doses are per 70 kg.
[2] 2-Choice Procedure = Hydromorphone 3 mg vs. placebo.
[3] 3-Choice Procedure = Hydromorphone 3 mg vs. Pentazocine 45 mg vs. placebo.

precise and refined characterizations of abuse liability are likely to result from multiple-choice drug discrimination procedures that characterize test drugs in relation to several reference training drugs.

Fourth, animal laboratory data indicate that more precise or specific discriminations, with a narrower range of generalization, tend to be established with higher doses of the training drugs (Over-ton 1984). The traditional method of assessing abuse liability by evaluating the acute profile of drug effects has been validated in procedures that typically use doses several times the therapeutic level. It seems likely that the drug discrimination procedure may also be most applicable to abuse liability assessment when comparably large doses are used. For example, in the Chait et al., studies of anorectic drug discrimination discussed earlier, the relatively low dose of *d*-amphetamine used, and its borderline discriminability from placebo, may have contributed to broad generalization of the amphetamine drug stimulus to nonabused anorectics. That the oral dose of 10 mg d-amphetamine was of borderline discriminability from placebo is indicated by the fact that of the 64 subjects trained in those studies only 52 percent successfully learned it. More distinctively different training drugs might have resulted in a more specific discrimination with less generalization to other drugs. In the opioid drug discriminations in our laboratory and in the other drug discriminations summarized earlier, which have used relatively larger training doses, approximately 90 percent of subjects have correctly learned the trained discriminations. Studies demonstrating the establishment of drug discrimination between two doses of the same drug (e.g., Colpaert and Janssen 1986) illustrate that the stimulus properties of drugs change as dose changes. Since drug abusers typically use greater than therapeutic doses it seems likely that it is the stimulus properties of these larger doses that will be most relevant to abuse liability.

CONCLUSIONS

The drug discrimination methodology is one that has proven its utility in the animal laboratory. There it appears that drugs with similar pharmacological actions or mechanisms share stimulus properties- i.e., they are discriminated as being similar to one another. Application of the drug discrimination methodology to human testing remains relatively novel. Here also we believe the drug discrimination methodology will have great utility, although insufficient data are yet available to clarify the full extent of its application and value.

In the work conducted thus far with humans, it is clear that drug discriminations with a wide range of different drug classes can be readily and rapidly learned by human volunteers. Also, it is clear that the procedure is compatible with concurrently collecting a broad array of subjective and physiological measures as is done in traditional assessments of the profile of acute effects. Yet, interpretation of the array ofthesetraditionalmeasures is often complicated. Drug discrimination procedures appear to provide a convenient method that can aid in more precise and refined differentiations among, and characterizations and categorizations of the nature of the effects of psychopharmacological agents.

Drug discrimination performance is not a direct index of abuse liability; but by aiding in the precise assessment of the similarities and differences among compounds the procedure can provide an improved estimation of the likely abuse potential of test compounds.

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CHAPTER 7

Abuse Liability of Anxiolytics and Sedative/ Hypnotics: Methods Assessing the Likelihood of Abuse

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Roland R. Griffiths, Ph.D.

INTRODUCTION

Drug abuse is a culturally-defined term referring to a socially unapproved pattern of drug self-administration behavior. Two important characteristics of the drug which influence the cultural definition(s) of drug abuse are whether the drug maintains self-administration and whether this self-administration occurs in a pattern that is injurious to the individual or society. Assessments of abuse liability therefore involve evaluations of both the potential for drug self-administration and the potential for deleterious consequences of drug use. These assessments correctly use the term, abuse liability, since definitions of "liability" include both the concept of likelihood as well as the concept of hazard or disadvantage.

There are certainly amultiplicity of factors influencing whether a particular drug will be defined as or become an abused substance including cultural and socioeconomic factors as well as pharmacological variables. Laboratory studies of abuse liability generally have focused on the pharmacological variables which may differentiate individual drugs with respect to their abuse liability. In humans, laboratory studies generally have attempted to predict the abuse liability of a particular test drug by examining the physiological and behavioral changes produced by the test drug in comparison to a standard drug with known abuse liability. This chapter will briefly discuss and illustrate the methods used in humans, to assess the abuse liability of drugs having a sedative profile (i.e., both anxiolytics and sedative/hypnotics). The emphasis of this chapter will be on those methods used to predict the likelihood of abuse although the value of simultaneous assessments of performance impairment as a deleterious consequence will be discussed as well. Basic principles involved in meaningful assessments will be emphasized and issues related

to the predictive validity of these methods will be discussed. A final section will outline a proposed course for abuse liability assessment in the development of new anxiolytics and sedative/hypnotics.

METHODS ASSESSING THE LIKELIHOOD OF SEDATIVE ABUSE

In humans, the likelihood of abuse usually is predicted through the use of one of two basic methods employed in subjects with histories of drug abuse. The most common method involves examination of the drug-induced profile of subject ratings such as ratings of drug liking, positive mood or euphoria. These subject ratings usually are assumed to reflect the subjective experience or psychoactivity produced by the drugs. Subject ratings are used to predict the likelihood of abuse with the assumption that the subjective mood changes produced by a drug may contribute to the likelihood of self-administration behavior. The second and most face valid approach involves a direct measure of the ability of drugs to reinforce drug self-administration. The reinforcing effects of a drug refer to its ability to increase the probability of behavior resulting in the administration of the drug. Studies in several laboratory animal species have shown that drugs can serve as reinforcers and maintain drug self-administration behavior much like food or water delivery serve to reinforce behaviors leading to their presentation. Such reinforcing effects of drugs are a major determinant influencing the likelihood that a particular drug will be abused. It is not clear how well subject ratings correlate with the reinforcing effects of drugs and a causal relationship cannot be assumed. Although both methods have face validity, the predictive validity of either human methodology has not been fully demonstrated.

SUBJECT RATINGS INDICATING A LIKELIHOOD OF ABUSE

Addiction Research Center Inventory (ARCI): The Addiction Research Center Inventory (ARCI) has been the subject rating scale most widely used to assess the subjective effects and abuse potential of psychoactive drugs. It is an empirically-developed true/false questionnaire from which subscales were derived based upon the subjective responses to seven different psychoactive drugs of male narcotic addict prisoners at the Addiction Research Center in Lexington, KY (Haertzen, 1966). These scales have been widely used to assess analgesics for morphine-like abuse potential (Fraser and Jasinski 1977; Jasinski et al., 1977). The MBG scale is comprised of those item responses produced by morphine and

amphetamine (benzedrine) and is often considered a euphoria scale. The PCAG scale is considered a sedative scale comprised of those items affected by the sedatives pentobarbital, chlorpromazine and alcohol.

Researchers utilizing the ARCI scales to assess the abuse liability of sedatives have obtained variable results. Of the ARCI scales, the PCAG scale is the most reliably affected by sedative drugs. In narcotic addicts, the PCAG scale has been increased by secobarbital, pentobarbital and phenobarbital (Fraser and Jasinski 1977). In sedative abusers, the PCAG sedation scale has been increased by pentobarbital (McLeod and Griffiths 1983; Griffiths et al., 1983), methaqualone (Cole et al., 1982b), diazepam (Griffiths et al., 1983; 1984b) and prazepam (Cole et al, 1982b). However, since chlorpromazine, which is not a drug of abuse, also increases ratings on this scale (Haertzen 1966), PCAG scale increases do not indicate a potential for abuse. The effects of sedatives on the MBG scale have been much less consistent. In narcotic addicts, secobarbital and pentobarbital have increased MBG ratings (Fraser and Jasinski 1977). In sedative abusers, increased MBG ratings have been observed with pentobarbital (Griffiths et al., 1983) and diazepam (Griffiths et al., 1983; 1984b). However, experiments have alsoreported failures to increase MBG ratings with pentobarbital (Haertzen 1966; McLeod and Griffiths 1983), phenobarbital (Fraser and Jasinski 1977) and diazepam and oxazepam (Griffiths et al., 1984a). While failures to increase the MBG scale sometimes have been suggested to indicate a lack of euphoria and abuse potential, it should be recognized that the MBG scale originally was derived from those items which discriminated morphine and amphetamine fromsedatives such as pentobarbital and alcohol which did not significantly affect this scale (Haertzen 1966). The lack of consistent effects on the MBG scale with pentobarbital, a standard sedative with known abuse potential, certainly reduces its value as an indicator of sedative abuse potential.

In anattempt to improve the sensitivity of the ARCI for sedative/hypnotic abuse potential assessment, a subset of items from the MBG and PCAG scales were selected (Jasinski et al., 1977) to derive new euphoria and sedative scales. In that report, pentobarbital, secobarbital, phenobarbital and methaqualone each produced dose-related increases on the modified euphoria scale. In subsequent reports, diazepam and chlordiazepoxide also produced dose-related increases in the euphoria scale (Jasinski et al., 1982) although the chlordiazepoxideeffect did not replicate in a subsequent study (Jasinski et al., 1983). Other researchers have reported variable results with this euphoria scale. In one study, methaqualone did but single low doses of diazepam and prazepam did not significantly increase ratings on the euphoria scale (Cole et al., 1982b). In another study, diazepam produced dose-related increases in euphoria ratings but

halazepam did so only minimally at a lower dose (Jaffe et al., 1983). Finally, Cole et al. (1982a) used a seven-point rating scale with the ARCI items to derive new euphoria and abuse potential scales which have not been further tested.

Subject Ratings of Drug Liking: In subjects with histories of sedative drug abuse, subject ratings on graded scales indicating that subjects "like" the effects of the drug reasonably suggest that the drug has some likelihood of abuse. In addition to the ARCI, researchers at the National Institute on Drug Abuse (NIDA)/Addiction Research Center employed subject ratings of drug liking from the single-dose opiate questionnaire in their sedative studies (Fraser and Jasinski 1977; Jasinski et al., 1977). These studies demonstrated dose-related increases in subject ratings of drug liking produced by secobarbital, pentobarbital, phenobarbital and methaqualone in subjects under the influence of these drugs. In a series of studies with sedative abusers, Griffiths and colleagues (McLeod and Griffiths 1983; Griffiths et al., 1980; 1983; 1984a,b) employed five-point rating scales with qualifying phrases associated with each response and showed that pentobarbital, diazepam and oxazepam produced dose-related increases in subject ratings of drug liking. Notably, changes in these drug liking ratings were more consistently observed than were changes in MBG ratings (McLeod and Griffiths 1983; Griffiths et al., 1980; 1984a). Subsequent studies (Roache and Griffiths 1985; 1987) extended these observations by showing dose-related increases in drug liking ratings by subjects under the influence of triazolam, lorazepam and meprobamate. These studies also employed analog line rating scales which were given to subjects on the morning of the next day and were to be completed with reference to the previous days' drug effect, Dose-related increases in next day ratings of drug liking were obtained withpentobarbital, triazolam, lorazepam and meprobamate. These next day ratings of drug liking may be important in that they may reflect the overall liking of the remembered drug experience and may predict the likelihood of future drug use better than ratings obtained while subjects are under the influence of the drug. All of the above mentioned studies employed urn-directional liking measures which ranged from no liking to an extreme specified by an adjective describing much liking. However, bi-directional liking measures ranging from dislike to neutral to like have also been employed. One study in alcoholics (Jaffe et al., 1983), reported difficulties in the analysis of the bipolar liking scale so the authors converted the data to fit two uni-directional dimensions of liking and disliking.

OTHER MEASURES INDICATING LIKELIHOOD OF ABUSE

Other measures have been employed which intuitively seem related to the abuse potential of a drug. One such measure is the subject's estimate of the monetary street value of the drug. In sedative abusers, dose-related increases in estimated street value have been observed with diazepam but not oxazepam (Griffiths et al., 1984b), with triazolam and pentobarbital (Roache and Griffiths 1985), and with lorazepam and meprobamate (Roache and Griffiths 1987). Cole et al. (1982a) also reported significant estimates of street value for diazepam and methaqualone and correlated these estimates with items from the ARCI to derive a new abuse potential scale. Another measure which has been used is a direct inquiry of the likelihood of future use. These ratings have been collected on a uni-directional visual analog line of "would choose again" (Roache and Griffiths 1985; 1987) and a bi-directional analog line of "would use/ never use again" (Cole et al., 1982a). Subjectwrittencommentsabout the effects of the drug also have been used to compare the abuse liability of diazepam and oxazepam (Griffiths et al., 1984b) and diazepam and triazolam (Roache and Griffiths 1988). One other measure which has been used to make inferences regarding abuse liability is classification, by experienced drug abusers, of the drug administered under double-blind conditions. In several studies (Roache and Griffiths 1985; 1987; Griffiths et al., 1984a,b; Jasinski et al., 1977) the differential classification of sedatives as belonging to either the barbiturate or benzodiazepine drug classes provided information regarding abuse liability to the extent that drugs perceived as barbiturate-like may have a greater likelihood of abuse.

POSITIVE AND NEGATIVE MOOD CHANGES

On an intuitive basis, it is sometimes assumed that drugs producing positive subjective mood changes would have a greater likelihood of self-administration than drugs which produce negative mood changes. Inferences regarding abuse liability have been made on the basis of positive or negative subjective mood changes. In the development of the ARCI, an LSD scale was derived from those items affected by LSD (Haertzen 1966). This LSD scale as well as a modified dysphoria scale have been employed in abuse liability studies to assess dysphoric effects of sedatives (Jasinski et al., 1977); however, significant dysphoric effects of sedatives have not been routinely described by other investigators. Significant dysphoric effects of buspirone in combination with reduced euphoric effects have supported the suggestion that buspirone has a reduced likelihood of abuse in comparison to diazepam (Cole et al., 1982a). A deterioration of mood and social behavior observed with diazepam but

not pentobarbital was suggested to contribute to lower abuse liability of diazepam (Griffiths et al., 1983).

MEASURES OF REINFORCING EFFECTS: DRUG SELF-ADMINISTRATION

Multiple Daily Dose Ingestion Procedures

Griffiths and colleagues (Bigelow et al., 1976; Griffiths et al., 1976; 1979) have employed procedures in which multiple ingestions per day of unit doses of pentobarbital or diazepam were available to subjects with histories of sedative abuse contingent upon completion of an exercise bicycle riding response requirement. These studies have shown that in subjects with histories of sedative abuse, sedatives are self-administered in a controlled laboratory environment. Furthermore, these studies collectively have shown that number of self-ingestions is an orderly function of dose, response requirement and inter-ingestion interval. The latter of these studies (Griffiths et al., 1979) employed double-blind placebo-controlled procedures in which, over an 8.5 hr period each day, subjects could self-administer up to ten ingestions of letter-coded doses of placebo, pentobarbital (30 or 90 mg/ingestion), diazepam (10 or 20 mg/ingestion) and chlorpromazine (25 or 50 mg/ingestion) across a ten consecutive day period. On the first day, subjects were encouraged to ingest a sufficient number of doses to sample the effects of that drug dose, however, the number of ingestions on this and all subsequent days were completely determined by the subjects. Figure 1 shows the mean number of ingestions per day for each of the dose conditions. Clearly, placebo and chlorpromazine failed to maintain self-administration since the rates of self-administration rapidly declined to near zero levels. In contrast, diazepam and pentobarbital produced dose-related increases in the number of daily ingestions. Pentobarbital produced overall greater and more stable rates of self-administration than diazepam which produced submaximal and gradually declining rates of self-administration across the ten days. These results are consistent with the suggestion that diazepam is less reinforcing than pentobarbital but more reinforcing than chlorpromazine. The use of chlorpromazine in this study illustrates the value of a negative control agent and demonstrates the sensitivity of the procedure to discriminate between drugs having definite abuse potential (e.g., pentobarbital) and drugs having very little or no abuse potential (e.g., chlorpromazine).

Two studies (Healey and Pickens 1983; Pickens et al., 1977) examined sedative self-administration in male and female subjects who were

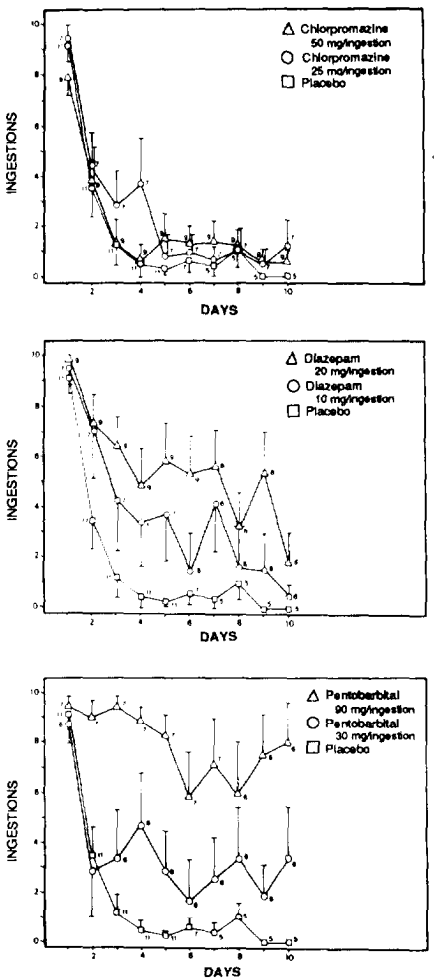

Figure 1: *Daily self-administration of placebo, chlorpromazine, diazepam and pentobarbital. Y-axes: No. of ingestions. X-axes: Ten consecutive experimental days. Data are mean (± S.E.M.) number of ingestions consumed each day for placebo, chlorpromazine (25 and 50 mg/ingestion), diazepam (10 and 20 mg/ ingestion), and penfobarbital (30 and 90 mg/ingestion). Numerals indicate the number of subjects tested each day. Reprinted from, Griffiths et al., 1979, J Pharmacol Exp Ther 210:303-310, 1979, with permission from Am. Soc. for Pharmacology Exp. Therapeutics.*

presumably physically-dependent on sedatives and were living on a psychiatric research unit. These studies utilized a concurrent access schedule in which subjects had concurrent ad libitum access to two alternative drug doses with a minimum inter-ingestion interval of 30 minutes. The first study (Pickens et al., 1977) examined relative preferences for varying doses of pentobarbital which were concurrently available. The authors concluded that subjects generally preferred intermediate doses (50-150 mg) over the high (200 mg) or low (30 mg) doses of pentobarbital. The second study (Healey and Pickens 1983) examined varying doses of diazepam (2-20 mg/ingestion) currently available with either diazepam (5 or 20 mg/ingestion) or pentobarbital (30 or 50 mg/ingestion). Dose-related effects of diazepam were only observed in some subjects. The significance of these studies to abuse liability assessment is not clear. The lack of a placebo control limits conclusions regarding relative reinforcing effects and consistent dose relationships were not reliably observed.

A recent study (Roache et al., 1988) employed a concurrent access procedure in which differently-colored capsules containing placebo or varying doses of triazolam were available by verbal request over a 3 hr period with a 10 min minimum interingestion interval. This preliminary study reported results in only three non-dependent male subjects with histories of sedative abuse. Generally stable levels of triazolam (0.125 mg/ingestion) self-administration were observed across a ten day period and variations in the triazolam dose (0.0312-0.25 mg) showed that the number of ingestions per day was inversely related to triazolam dose. The use of the concurrently-available placebo in this report allows the conclusion that triazolam maintained self-administration behavior in this concurrent access procedure.

Single Daily Dose Ingestion Procedures

Choice procedures have been used to provide a direct measure of the relative preference for single doses of each of two available alternatives. In order to directly compare the relative preference for different doses of pentobarbital and diazepam, subjects with histories of sedative abuse who were living on a research ward were given multiple independent discrete choices between two available alternatives under double-blind conditions (Griffiths et al., 1980). Subjects preferred high doses of both pentobarbital and diazepam over placebo and preferred higher doses of pentobarbital over lower doses. This study also showed that 400 mg pentobarbital was preferred over 200 mg diazepam, however, the fact that only single doses were tested precludes conclusions regarding the relative reinforcing effects of the two drugs. A subsequent study (Griffiths et al., 1984b) utilized similar procedures and varied the dose of diazepam

which was available as an alternative to a high dose of oxazepam (480 mg). Figure 2 shows that diazepam produced dose-related increases in the number of subjects choosing diazepam over oxazepam. Conclusions from this study would have been more definitive if varying doses of oxazepam were compared to diazepam. However, the diazepam dose-response function permitted an estimation that diazepam may be eight times more potent than oxazepam in its relative reinforcing effects. This eight-fold potency difference in reinforcing effects was consistent with potency determinations from other measures indicating likelihood of abuse including MBG ratings and ratings of drug liking and street value. This eight-fold potency difference on measures of likelihood of abuse was contrasted with the fact that, in clinical use and in measures of psychomotor impairment, diazepam is only three times more potent than oxazepam.

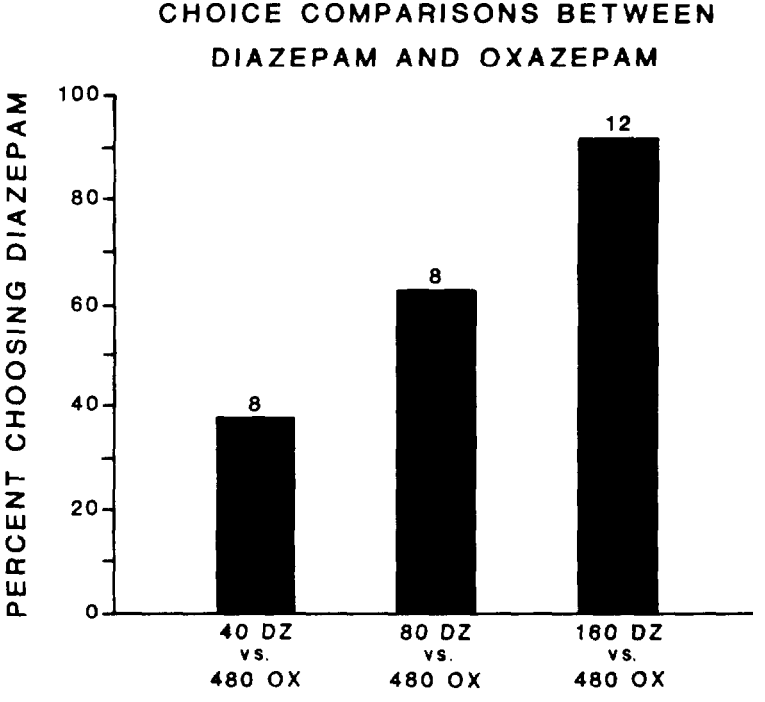

Figure 2: *Diazepam dose preference over oxazepam. Y-axis: Percentage of subjects choosing diazepam (DZ) over oxazepam (OX) in three separate choice comparisons. X-axis: Three separate choice comparisons of 40 mg OX vs. 480 OX; 80 mg DZ vs. 480 OX; and 160 mg DZ vs. 480 mg OX. Numerals indicate the number of subjects tested in each choice comparison. Reprinted from, Griffiths, et al., 1984b, J Pharmacol Exp Ther 229:501-508, 1984, with permission from Am. Soc. for Pharmacology Exp. Therapeutics.*

Two other studies have employed methods in which subjects, with histories of sedative abuse who were living on a research ward, were allowed to choose whether or not to receive a single letter-coded drug dose which they had sampled on a previous occasion. One study (McLeod and Griffiths 1983) employed a progressive ratio schedule in which subjects had to press buttons or ride an exercise bicycle to complete progressively increasing response (work) requirements in order to receive placebo or various doses of pentobarbital. The results showed that the amount of work subjects engaged in was an orderly function of pentobarbital dose; higher doses maintained greater response ratios and therefore, were presumably more reinforcing. Another study (Roache and Griffiths 1988) employed a progressively increasing bicycle riding requirement in order for subjects to self-administer single doses of diazepam (40 or 80 mg), triazolam (1.0 or 2.0 mg) or placebo across a 6 day period. Both diazepam and triazolam were self-administered on more occasions and by more subjects than placebo which was self-administered by only one subject on only two occasions. Across the six day period, the bicycle riding requirement was progressively increased from 30 to 180 minutes and the number of subjects choosing to self-administer drug decreased for both drugs. Nodifferences in the reinforcing effects of diazepam and triazolam were detected in this study.

CORRESPONDENCE BETWEEN SUBJECT RATINGS AND SELF-ADMINISTRATION

The recent study (Roache and Griffiths 1988), which compared the self-administration of single doses of diazepam (40 or 80 mg) and triazolam (1.0 or 2.0 mg), provided an opportunity to compare the subject ratings obtained on initial drug exposures with subsequent drug self-administration behavior. Following an inital sampling exposure to a letter-coded drug under double-blind conditions, subjects chose whether or not to receive that same drug on each of the next six consecutive days. Both diazepam and triazolam were self-administered by all eight subjects on the first self-administration opportunity. However, there were differences in the total number of occasions each subject self-administered diazepam and triazolam across the six days of availability. Various subject ratings were compared to the subjects' self-administration behavior to examine the correspondence of these two methods which are used for abuse liability assessment. Figure 3 shows that subject ratings of drug liking obtained on the morning of the day following the first occasion of self-administration was significantly correlated with the total number of occasions subjects subsequently self-administered each drug. Because of the small sample

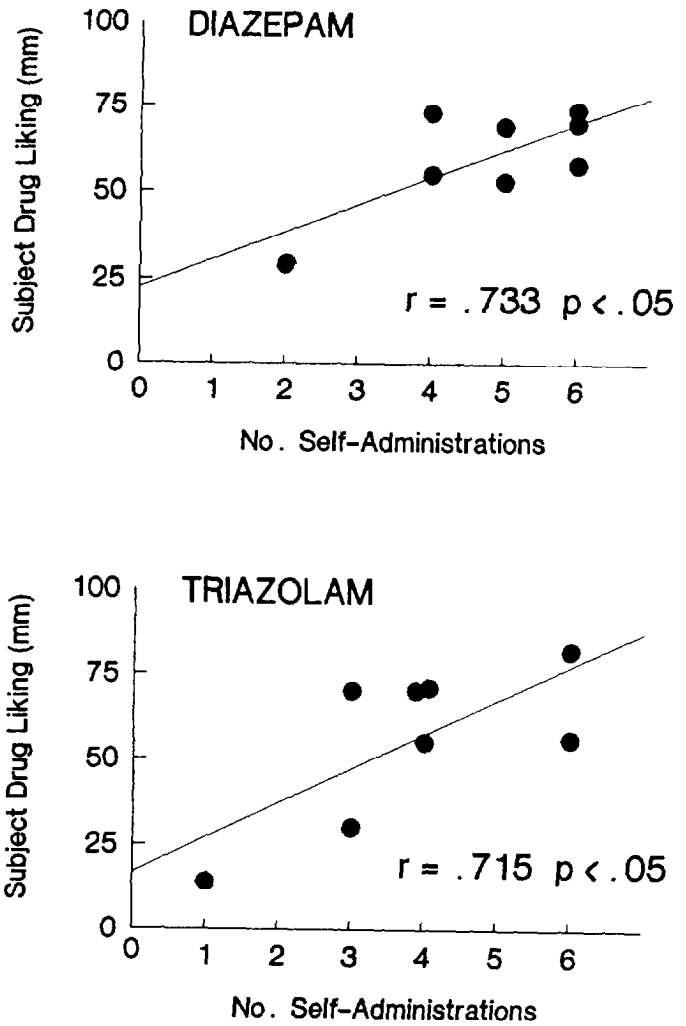

Figure 3: *Correlations of self administration and subject ratings of drug liking for diazepam and triazolam. Y-axes: Millimeter scores from a 100 mm analog rating scale for drug liking. X-axes: No. of occasions of self-administration. Circles represent coordinate point data for each of eight subjects who were provided separate opportunities to self-administer diazepam and triazolam on a maximum of six occasions across six consecutive days. Also shown are the regression lines of y on x, correlation coefficients and p-values determined by linear regression. Subject ratings of drug liking were collected on the morning of the day following the first occasion of self-administration. Reprinted from, Griffiths et al., 1979, J Pharmacol Exp Ther 210:303-310, 1979, with permission from Am. Soc. for Pharmacology Exp. Therapeutics.*

size and the limited number of doses tested, these results should be considered preliminary. However, they demonstrate procedures which may be of value in examining the relationship of reinforcing effects and subject ratings and suggest that a positive relationship may indeed exist.

A series of studies conducted in student and employed male and female volunteers without histories of drug abuse have provided many insights into the relationship between subject ratings and reinforcing effects. These studies examined the reinforcing effects of sedatives and stimulants in subjects who were not maintained in laboratory environments but were allowed to leave the laboratory and go about their daily routines following drug ingestion. The procedures involved initial double-blind sampling of color-coded placebo or drug capsules and five subsequent choice trials between the drug or placebo alternatives. These studies have shown that stimulants such as amphetamine were self-administered but sedatives including diazepam (Johanson and Uhlenhuth 1980), lorazepam (de Wit et al., 1984a) and flurazepam (de Wit et al., 1984b) generally were not self-administered. In a modified procedure (de Wit et al, 1984c), the same subject population was maintained in the laboratory following evening drug administration; however, diazepam and pentobarbital self-administration was not observed. In these studies, the benzodiazepines generally increased PCAG sedation ratings but not MBG euphoria ratings (de Wit et al., 1984a,b). Although pentobarbital increased MBG ratings (de Wit et al., 1984c), it also was not chosen over placebo. Although reinforcing effects of sedatives generally have not been detected in these procedures, a review of several studies conducted with amphetamine and diazepam reported that a minority of subjects did in fact prefer diazepam over placebo (de Wit et al., 1986b). In this review, the tendency for subjects to choose drug over placebo was associated with drug-induced subject ratings on the Profile of Mood States (POMS). Subjects choosing amphetamine over placebo tended to show greater positive mood changes than non-choosers and subjects choosing diazepam over placebo have tended to show lesser sedative effects of diazepam than those choosing placebo. These studies also have used bidirectional drug liking scales. Although liking scores were not presented, tendencies for drug choosers to like drug better than placebo and for placebo choosers to like placebo better than drug were reported. These results suggest that the drug self-administration patterns of individual subjects may be related to their subjective response to drugs as revealed by subject ratings of mood and drug liking.

EXPERIMENTAL DESIGN CONSIDERATIONS

The Validity of Methods Suggesting Differences Between Drugs

Using these methods of abuse liability assessment, predictions regarding the likelihood of abuse of various sedatives seem reasonable based upon the face validity of the measures of drug-induced subjective effects and self-administration. However, the predictive validity of these methods has not been established due to a general lack of studies evaluating drugs which could serve as negative controls (i.e., drugs clearly lacking abuse liability). For these reasons, confidence in predictions of the likelihood of abuse will be improved as methods are better developed and a larger variety of drugs are tested under a wider range of conditions. The demonstrated value of these methods has been in the description of quantitative differences between various sedative drugs using measures which are clearly sensitive to effects of standard drugs of abuse. Conclusions regarding quantitative and qualitative drug differences have been possible in studies which examined the effects of a range of doses of the test compound in comparison to a standard drug using measures which were sensitive to the effects of the standard drug. Additional confidence in conclusions of drug differences has been gained through the use of a multiplicity of measures and systematic replication of experimental results under different conditions.

As noted in two reviews on the abuse liability of benzodiazepines (Griffiths and Roache 1985; Woods et al., 1987), experiments testing a range of doses with a variety of procedures and measures have reasonably demonstrated differences in the abuse liability of various sedatives. Several studies have shown that diazepam and other benzodiazepines, have a lesser likelihood of abuse than pentobarbital andmethaqualone (Griffiths and Roache 1985). The conclusion that benzodiazepines have a lower abuse liability than many other barbiturate and non-barbiturate sedatives is supported by the variety of experimental procedures suggesting this conclusion and is also supported by epidemiological data indicating a lower prevalence of benzodiazepine abuse (Woods et al., 1987). The best demonstration of differences among the benzodiazepines has been in two studies suggesting that oxazepam has a lesser likelihood of abuse than diazepam (Griffiths et al., 1984a,b). This conclusion, based upon laboratory studies of abuse liability, is supported by data from the United States (Griffiths et al., 1984b) and Sweden (Bergman and Griffiths 1986) which suggest that diazepam abuse uniformly exceeded oxazepam abuse on several epidemiological measures of drug abuse. The latter report demonstrated that this conclusion is not an artifact of differential prescription frequencies of diazepam and oxazepam which have similar

prescription rates in Sweden. The validity of human self-administration methodologies in sedative abusers is supported by one study (Griffiths et al., 1979) which showed that diazepam was self-administered to a lesser extent than pentobarbital but to a greater extent than chlorpromazine. This study is an example of the use of a negative control drug to validate conclusions since chlorpromazine is generally accepted to have very little or no potential for abuse.

The validity of sedative abuse liability assessment methods is supported by these above-mentioned studies which have developed these methods by testing drugs with known abuse liability profiles. The predictive validity of these methods will be tested as new drugs under development are correctly categorized by these methods as to their abuse liability. Buspirone represents one such new drug which has been predicted to have a reduced likelihood of abuse in comparison to diazepam (Cole et al., 1982a). However, this study must be considered preliminary since it examined only two doses of buspirone. This limited human evidence for a reduced abuse liability of buspirone is often accepted less critically than would otherwise be true since buspirone has a novel chemical structure and pharmacological profile and does not potentiate ethanol (Ortiz et al., 1987) and is not self-administered by monkeys (Balster and Woolverton 1982).

Concurrent Measures of Drug Effect and Performance

The quantitative measurement of drug effects other than those specifically related to predictions of the likelihood of abuse can be of great value in abuse liability assessment studies for several reasons. First, it is important to have such concurrent measures in order to demonstrate that adequate and comparable doses of the test compound have in fact been employed in the study. This is particularly important if the test compound lacks effects on the measures of the likelihood of abuse. Second, comparisons of dose-response functions and relative potency differences between the standard and test compounds across different measures strengthen any conclusion that the test compound is or is not different in its likelihood of abuse. Finally, these concurrent measures can be used to simultaneously assess the deleterious consequences or the relative advantage of the test compound in comparison to the standard drug. In order to strengthen conclusions regarding drug comparisons, several studies have employed concurrent measures including observer ratings of drug effect magnitude and objective measures of psychomotor and cognitive performance.

The power of the use of concurrent measures in an acute dose-response study is illustrated in figure 4. This study (Roache and Griffiths 1985) compared placebo and a six-fold range of triazolam and pentobarbital

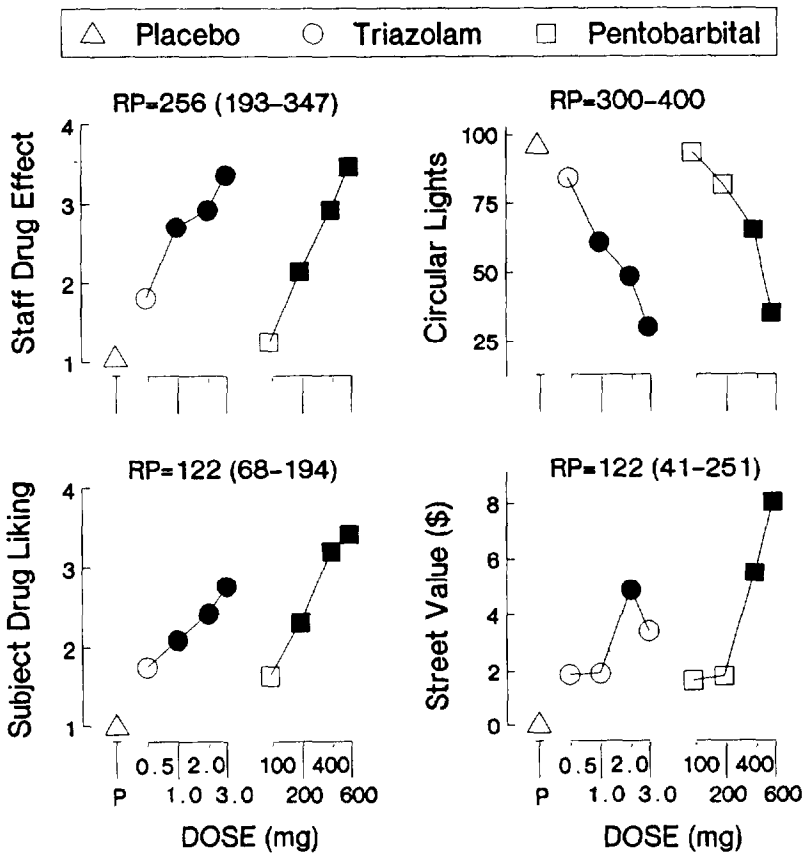

Figure 4: *Triazolam and pentobarbital dose-response functions for staff ratings, psychomotor performance and subject ratings of drug liking and estimated street value. Y-axes: Peak ratings of staff-rated drug effect magnitude; peak degree of psychomotor impairment (percent of pre-drug) on the circular lights task; peak degree of subject-rated drug liking; and subject-estimated street value ($). X-axes: Triazolam and pentobarbital dose (mg); "P" designates the placebo dose. The relative potencies (RP) and 95 percent confidence limits (C.I.) are shown above each panel exceptfor circular fights which shows an estimate of relative potency since the data did not meet the criteria for relative potency determination. Data are means of nine subjects tested at each dose condition. Darkened symbols indicate data points significantly different ($p < 0.05$) than placebo, Duncan's Multiple Comparisons Procedure. Reprinted from, Griffiths et al., 1979, J Pharmacol Exp Ther 210:303-310, 1979, with permission from Am. Soc. for Pharmacology Exp. Therapeutics.*

doses using a within-subject cross-over design. The upper two panels show that triazolam and pentobarbital produced comparable effects to increase staff (observer) ratings of drug effect magnitude and to impair circular lights (psychomotor) performance. In contrast, triazolamproduced lesser effects than pentobarbital on subject ratings of drug liking and next day estimates of street value. The relative potency of 256 on staff drug effect ratings indicates that 256 mg of pentobarbital produced the same effect as 1 mg triazolam on this measure. The lower relative potencies (i.e., RP=122) on measures indicating likelihood of abuse indicate that it took less pentobarbital (only 122 mg) to produce the same effect as 1 mg of triazolam. Thus, the relative potency differences across these measures indicate that at doses which produce comparable degrees of drug effect and psychomotor impairment, triazolam would be less well liked and have lower street value than pentobarbital. Clearly, the examination of a range of doses of both drugs which are demonstrated to be comparable on concurrent measures, strengthens conclusions regarding a reduced likelihood of abuse of triazolam relative to pentobarbital.

Other studies have strengthened conclusions regarding drug comparisons by employing concurrent objective measures of psychomotor and cognitive performance. In a comparison of diazepam and oxazepam (Griffiths et al., 1984a), a greater potency difference between the two drugs was observed with measures predicting the likelihood of abuse than with measures of psychomotor impairment. These relative potency differences indicate that oxazepam has a lower likelihood for abuse than diazepam at doses which produce comparable degrees of psychomotor impairment. Another study (Roache and Griffiths 1987) reported that lorazepam was relatively less potent than meprobamate in producing subject-rated drug liking at doses which produced comparable degrees of psychomotor impairment. The concurrent measures utilized in the comparisons of triazolam and pentobarbital (Roache and Griffiths 1985) and lorazepam and meprobamate (Roache and Griffiths 1987) showed that triazolam and lorazepam had a greater potential than pentobarbital and meprobamate to produce amnestic effects and impair the subjects' recognition of their own impairment. Overall, these studies have described a profile of behavioral effects of benzodiazepines which are different than those seen with traditional barbiturate and non-barbiturate sedatives and anxiolytics. The profile indicates that in comparison to barbiturates and other sedatives, benzodiazepines have a lesser likelihood of abuse but a greater potential to produce certain types of performance impairment (Roache and Griffiths 1987).

Subjects and Laboratory Procedures

Most studies of sedative abuse liability assessment haveemployedsubjects with histories of sedative, alcohol and/or narcotic drug abuse who were maintained in residential laboratory environments (Fraser and Jasinski 1977; Griffiths et al., 1979; 1983; Jaffe et al., 1983). Other studies have employed college students with recreational sedative abuse histories who were maintained in laboratory environments for the day following drug ingestion (Cole et al., 1982a,b). However, several studies assessing the reinforcing effects of benzodiazepines in normal subjects have utilized student and employed volunteers who did not remain in the laboratory but continued their normal daily routines following drug ingestion (Johanson and Uhlenhuth 1980; de Wit et al., 1984a,b; 1985; 1986b). Reinforcing effects of pentobarbital and diazepam clearly have been demonstrated in subjects with histories of sedative abuse living in residential laboratory environments (c.f., Griffiths and Roache 1985). In contrast, reinforcing effects of diazepam generally have not been observed in normal subjects who were not maintained in controlled laboratory environments (de Wit et al., 1985; 1986b). It is not clear whether the critical determinants of these discrepant observations are subject drug history or environmental context (Johanson and Uhlenhuth 1980). Both history and environmental variables have been shown to influence the reinforcing effects of benzodiazepines in laboratory animals (Ator and Griffiths 1987; Bergman and Johanson 1985). Several studies have investigated procedural variables possibly influencing the lack of reinforcing effects of diazepam in the normal volunteer studies. One study (de Wit et al., 1985) found that experimental variations in subject age and the time of day of drug administration did not increase the reinforcing effects of diazepam. Another study (de Wit et al., 1986a) found that anxious subjects were no more likely to self-administer diazepam than werenormalcontrol subjects. Another modification required normal subjects to spend four hours in the laboratory following the evening ingestion of diazepam or pentobarbital (de Wit et al., 1984c). This latter study also did not detect reinforcing effects of diazepam or pentobarbital. Clearly, the inability to detect reinforcing effects of pentobarbital, a standard drug with known abuse potential, precludes the use of these procedures to quantify the abuse liability of sedatives having a likelihood of abuse which is equal to or less than that of pentobarbital.

A recent study (de Wit et al., 1988) modified the choice procedures previously used in normal subjects and demonstrated that diazepam did produce reinforcing effects in subjects with light (4.8 drinks per week) or moderate (11.8 drinks per week) histories of current alcohol use. Three

important procedural modifications employed in this study include: the specific recruitment of alcohol users; the creation of a social environment where subjects participated in social groups during evening sessions and were maintained in the laboratory over night; and the use of multiple dose ingestion choice procedures. In contrast to the mostly negative results in previous studies of normal subjects, this study suggested that benzodiazepines may be reinforcers in subjects without significant drug abuse histories under certain laboratory conditions. However, these data also suggest that subject drug history may influence the reinforcing effects of anxiolytics such as diazepam. Whereas diazepam was generally preferred over placebo in both populations, a greater proportion (100 percent vs. 61 percent) of the moderate drinkers self-administered higher doses (25.2 mg vs. 18.8 mg) of diazepam than did the light drinkers. Compared to the light drinkers, the moderate drinkers also had greater histories of marijuana, tobacco, hallucinogen and opioid use. The results of a series of early studies (Beecher 1959) suggested that subject drug history variables may also influence subjective responses to different drugs. In those studies, normal subjects and patients hospitalized for chronic disease rated amphetamine as producing a strong euphoric effect while heroin, morphine, pentobarbital and placebo were rated as less euphoric or unpleasant. In contrast, abstinent non-dependent narcotic addicts not only rated amphetamine as producing euphoria but also rated the opioids as producing euphoria. Thus, the ratings of subjects with opioid abuse histories reflected the potential for abuse of opioid drugs better than did the subject ratings of patients or normal subjects.

Overall, these data indicate that subject drug history variables may indeed be important in assessing abuse liability. There is a great deal of face validity in utilizing subjects with histories of drug abuse to determine whether one drug has a greater or lesser likelihood of abuse than another drug; for it is this population who will most likely abuse drugs having a potential for abuse. However, the development of new methods for studies in normal or light social drinkers may provide the opportunity to better assess the likelihood of abuse of sedatives and anxiolytics in non-abuser populations.

PRINCIPLES GOVERNING MEANINGFUL ABUSE LIABILITY ASSESSMENT

Based upon a review of existing methodologies for sedative abuse liability assessment, five basic principles have emerged which seem to impact one's ability to draw meaningful experimental conclusions regarding differences between individual compounds of the anxiolytic and sedative/ hypnotic drug classes.

Principle 1: Comparison to a Standard

A well established principle of any biological assay is that the unknown sample must be compared to a standard tested under the same assay conditions. In the biobehavioral assay of abuse liability assessment, this means comparing the test compound to a standard drug of known abuse liability under double-blind conditions. The best documented standard sedatives include pentobarbital, secobarbital and methaqualone. Depending upon what is known about the test compound and its planned indication(s), studies also may make comparisons to other drugs currently used for the same indication. In the case of benzodiazepines, diazepam would be considered the prototypic standard although lorazepam and triazolam have been reasonably well investigated.

Principle 2: Dose-Response Evaluation

In the abuse liability assay, one must examine a range of doses of the test compound as well as the standard drug to permit quantitative and qualitative conclusions. If only single doses of the standard and test compounds are evaluated, meaningful conclusions may not be possible. If a single dose of the test compound is compared to a range of doses of the standard, then at least one could determine quantitatively, where that specific dose falls on the standard curve. However, unless a meaningful range of doses of the test compound are tested, one can always argue that the doses were too low or too high. Another reason to test a range of doses is that higher than therapeutic doses are likely to be used by drug abusers so it is not sufficient to test only therapeutic doses. Qualitative and quantitative conclusions regarding a lack of or lesser abuse liability, respectively, are most likely possible in experiments examining a reasonable range of doses which are demonstrated to be comparable.

Principle 3: Concurrent Measures and Relative Potency Comparisons

In addition to examination of a range of doses, the simultaneous examination of concurrent measures of drug effect in addition to measures predicting the likelihood of abuse permits the demonstration of comparable doses. For example, doses could be selected which produce comparable effects on one dimension such as sedation, psychomotor or cognitive impairment, muscle relaxation, and hypnotic or anxiolytic activity. With demonstrated comparability on this standard dimension, conclusions regarding greater or lesser abuse liability at those comparable doses become meaningful. Relative potency estimations on the various concurrent measures are a useful standard statistical measure enabling comparisons across dimensions.

Principle 4: Systematic Replication

Although the available data obtained from abuse liability studies are reasonably consistent with clinical observation, the predictive validity of these methods has not been well established due to the limited range of conditions studied and a general lack of studies with drugs which could serve as negative controls (i.e., drugs clearly lacking abuse liability). Therefore, confidence in predictions of the likelihood of abuse will be improved as methods are better developed and a larger variety of drugs are tested under a wider range of conditions. For now, no single method can be identified as the best or most valid predictor of the likelihood of abuse. As is true for any experimental conclusion, one can have greater confidence in conclusions which are systematically replicated across a range of experimental conditions and dependent measures. Thus, studies can enhance the confidence of conclusions regarding the abuse liability of a test compound by utilizing a multiplicity of measures and experimental procedures.

Principle 5: Select Appropriate Subject Populations

The appropriateness of employing subjects with histories of drug abuse to predict the likelihood of abuse of new compounds is self evident; this is the population who would abuse a drug which has the potential for abuse. Studies which have reasonably demonstrated differences between individual sedatives and anxiolytics in regard to their abuse liability have predominately employed non-dependent sedative abusers and alcoholics. Most studies in normal non-drug abuser populations have not been able to distinguish among individual sedatives in regard to their likelihood of abuse and have not developed measures sensitive to standard drugs of abuse such as pentobarbital. A recent study in light to moderate alcohol users suggests the possibility that methods capable of differentiating between individual sedatives and anxiolytics may be developed in future studies of this or even more drug naive populations.

PROPOSED COURSE FOR THE ABUSE LIABILITY TESTING OF NEW DRUGS

Human studies of abuse liability assessment can occur anywhere within the course of development of a new sedative/hypnotic or anxiolytic. Of course, the ultimate design of any study will be influenced by the known pharmacological and safety profile of the new compound at the time of the study design. For example, studies conducted in the earlier Phase I or II development process may be limited to dose-ranging studies due to

limited information on human safety. Ultimately, however, valid conclusions regarding the abuse liability of a new compound can only be drawn if a meaningful range of doses of the new compound has been compared with standard drugs of known abuse liability. The following proposed course for abuse liability testing is general and idealized; the specific studies would depend on the specific drug under development and its known pharmcological profile. In addition to testing for the likelihood of abuse, the use of concurrent measures may allow some of these studies to serve dual purposes in the necessary Phase I and II safety testing and in the demonstration of pharmacological profiles of the new compound which may be favorable in comparison to frequently used compounds (e.g., reduced sedative or amnestic liability).

The initial study with any new compound should be a dose-ranging study in which various doses are administered acutely to evaluate the dose-response function of the drug on measures of abuse liability and concurrent measures as well. It would be preferable, at this point, to include a standard drug of known abuse liability in order to enhance the value of the study. In this and all studies of abuse liability, subject ratings used to predict the likelihood of abuse should be employed including euphoria and ARCI scales, drug-liking ratings, and possibly other measures of mood or subject ratings indicating likelihood of abuse.

Once there is confidence regarding appropriate dose selection, a more definitive study should compare an adequate range of doses of both the new and standard compounds using established procedures and measures of abuse liability. This study will typically be an acute dose-response evaluation employing several subject ratings indicating likelihood of abuse as well as concurrent measures such as subjective mood and/or objective measures of sedation and performance. Once the basic dose-response comparison to a standard is accomplished, several types of follow-up studies could be conducted to expand the generality of the findings. Follow-up studies may include repeated dose administration to examine tolerance phenomena or drug interaction studies (e.g., alcohol interactions) to assess potential polydrug abuse complications. Other studies may include a comparison of the new drug to other standard drugs of known abuse potential or to other drugs currently used for the probable therapeutic indication. Due to the face validity of studies examining drug self-administration behavior, another study may directly examine the reinforcing effects of the new compound as compared to a standard drug of known abuse liability. Because of the complexities of self-administration studies and the limited number of doses which can be feasibly tested, these studies should be considered only after undertaking thorough acute dose-response evaluations.

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CHAPTER 8

Drug Self-Administration Procedures: Alcohol and Marijuana

Nancy K. Mello, Ph.D.

INTRODUCTION

Traditionally, drug self-administration procedures have been used in animal models to evaluate the abuse liability of new drugs (Schuster and Johanson 1974; Griffiths et al., 1980, Brady and Lukas 1984). Although there are many variations on the basic experimental paradigm, usually the reinforcing efficacy of a new drug is compared to a standard drug of known abuse potential and to a placebo control in the same animal under the same conditions. The behavioral measures include the rate of response for drug injections, the number of drug injections taken, and in some instances, the number of responses an animal is willing to emit for a single drug injection. Comparison of these behavioral measures permits a rankordering of the new compound against placebo control and the standard drug with respect to relative abuse potential.

Clinical research on drug self-administration procedures has used very similar operant behavioral techniques. But the primary focus of clinical studies has usually been quite different from the animal studies of drug abuse liability insofar as human research subjects are given access to drugs that are known to be abused, such as alcohol, marijuana, opiates, stimulants or sedatives. Subjects are volunteers with a history of drug use or drug addiction and patterns of drug self-administration as well as the effects of drug intoxication are observed. Clinical studies usually are multidisciplinary and involve examination of a number of behavioral, biological and social variables before, during and after a period of self-regulated drug intoxication. Clinical drug self-administration studies are useful for the evaluation of new pharmacotherapies, as well as studies of the basic behavioral pharmacology of abused drugs and interactions between drugs. These applications of clinical drug self-administration studies are summarized below.

Pharmacotherapy Evaluation: Several new pharmacotherapies have been developed for the treatment of opiate abuse and evaluated under controlled research ward conditions. Recently the efficacy of naltrexone, an opiate antagonist, and of buprenorphine, an opioid mixed agonist-antagonist, for the pharmacologic treatment of opiate addiction has been examined in human drug self-administration studies (Meyer and Mirin 1979; Mello&., 198 1, 1982). Although medical considerations limited the number of heroin injections available each day, it was possible to examine the effects of naltrexone and of buprenorphine (with their respective placebos) on heroin self-administration (Meyer and Mirin 1979; Mello et al., 1981, 1982). Demonstration of the effectiveness of buprenorphine and naltrexone in suppressing heroin self-administration suggested the potential effectiveness of these drugs for outpatient treatment of opiate-dependent patients.

Behavioral Pharmacology of Drug Abuse: A second application of drug self-administration procedures in clinical studies is to examine the basic behavioral pharmacology of drug use and abuse under controlled research ward conditions. In studies of alcohol and marijuana, subjects were given unlimited access to drugs for several weeks while residing on a clinical research ward. Subjects worked at an operant task for alcohol or marijuana and a competing (non-drug) reinforcer such as money on concurrent schedules of reinforcement. Behavioral measures included rate of response, distribution of time spent working for drug and non-drug reinforcers, and number and temporal distribution of drug units (drinks, cigarettes) purchased.

One advantage of inpatient clinical studies is that drug use patterns and drug effects can be observed directly, rather than relying on anecdotal or retrospective reports. Hypotheses about drug effects and patterns of drug use based on "street lore" can be examined objectively. A vast discrepancy between a subject's recall of a drug intoxication experience and objective measures during drug intoxication has been consistently observed in a number of laboratories (see Mello 1983 for review). The observation that intoxication with alcohol and with opiates exacerbates rather than alleviates feelings of depression, despondency, dysphoria, and unworth greatly complicates our understanding of what is "reinforcing" about drug intoxication (Mello 1983, Mendelson and Mello 1985). Yet, drug self-administration persists despite increased despondency and anxiety. Clearly, simplistic concepts such as elevated mood and euphoria do not adequately characterize drug effects during chronic drug self-administration. These data complicate analysis and prediction of the reinforcing properties of psychoactive drugs and raise continuing questions about the nature of drug reinforcement.

Drug Interactions: Another advantage of inpatient clinical studies is that interactions between drugs can be studied. For example, the effects of intoxication with alcohol or opiates on tobacco smoking can be measured. Anecdotal reports that alcohol and marijuana act synergistically to enhance intoxication can be examined directly by studying concurrent use patterns. Since polydrug use appears to be an increasingly prevalent pattern (Kreek 1987, 1989), the concurrent drug self-administration paradigm should be especially valuable for determining how the availability of two or more drugs changes use patterns of a single drug.

The remainder of this review will describe basic techniques for the operant analysis of human drug self-administration. Recent findings from human drug self-administration studies will be summarized to illustrate selected types of behavioral analyses. Some possible applications of these procedures for drug abuse liability assessment in humans will be described. Finally, the concept of drug reinforcing efficacy and its implications for the assessment of abuse liability will be discussed.

OVERVIEW OF OPERANT PROCEDURES FOR STUDIES OF HUMAN DRUG SELF-ADMINISTRATION

In real life, drugs are not available without some expenditure of effort or money and operant work-contingent drug self-administration is one approach to simulating relatively unconstrained drug use patterns under clinical research ward conditions. Operant techniques to study human drug self-administration are derived from concepts and procedures for the experimental analysis of behavior first described by B. F. Skinner (Skinner 1938, 1953). Operant procedures permit direct observation of the amount and frequency of drug self-administration and the behavioral consequences of drug intoxication on operant performance.

A number of operant procedures have been used to examine human drug self-administration since 1965 and the conceptual and technical evolution of these techniques has been reviewed elsewhere (see Bigelow et al., 1975; Mello and Mendelson 1965, 1978, 1987). The feature common to all of these operant procedures is that subjects must emit responses on a specified schedule of reinforcement to obtain drugs or competing reinforcers such as money, television time, etc. In situations where subjects are given unlimited access to drugs, the pattern of drug self-administration can be operationally defined by the following measures:

(1) The number of drug self-administration occasions (per hour, per day, per week).
(2) The drug dose selected on each occasion (e.g., number of drinks, cigarettes or capsules.).
(3) The time of drug purchases within a day.
(4) The interval between successive drug self-administration occasions, i.e. the distribution of drug doses over an hour, a day, or a week.

Operant procedures produce orderly sequences of responding which in turn provide an objective index of the relative reinforcing consequences of drugs or of competing reinforcers, such as money, at any point in time. In situations where two drugs are available concurrently, effects of drug use on choices between these alternative drug reinforcers can also be examined to yield an index of relative reinforcing efficacy.

Although it is obvious that drug use and drug intoxication affect the subsequent pattern of drug self-administration, it is useful to distinguish between drug use patterns and *drug effects*. Behavioral measures of drug effects on subjective states, performance tasks, social interaction variables and the acquisition of non-drug reinforcers often complement evaluation of drug use patterns. One limitation of the study of spontaneous drug self-administration patterns is that precise time-dose-response relationships between various drug-effect variables cannot be established since the drug dose, frequency and inter-dose intervals will vary on an unpredictable basis. Yet, this variability constitutes the drug self-administration pattern which is the primary dependent variable in many studies of operant drug self-administration.

We have argued elsewhere that the pattern of drug self-administration is an important dependent variable which may be central to our understanding of human substance abuse. Basic behavioral pharmacology has repeatedly shown that the schedule of drug reinforcement, i.e., the dose and frequency of drug availability, influences the effects of drugs on behavior (Kelleher et al., 1976; Spealman et al., 1983). The self-imposed schedule of reinforcement can be examined in individuals given an opportunity to determine their own pattern of drug self-administration. Eventually, the comparison of drug self-administration patterns across drugs may help to identify some commonalities and differences in the proximal determinants of patterns of heroin abuse, alcohol abuse, marijuana and tobacco use, etc.

The schedule of *reinforcement* and the type of *operant manipulanda* are two basic factors which define any drug self-administration paradigm.

The schedule of reinforcement specifies the number and/or pattern of responses required for acquisition of a single drug dose or monetary unit. Time-based schedules, such as *Fixed Interval* or *Variable Interval schedules* are very useful in clinical research because time is the most relevant dimension on a clinical research ward. Time based schedules specify that only the first response emitted after a fixed or variable time interval counts as an "effective" response towards drug acquisition. Ratio schedules require a specified number of responses for reinforcement. *Fixed* or *Variable Ratio schedule* response requirements can often be completed in a few minutes (depending upon the operant manipulanda) and there is no uniformity within or between subjects in duration of operant responding. Ratio and Interval schedules can also be combined to form multiple schedules. In a multiple schedule, completion of each component is required for reinforcement. If a stimulus (light or sound) is presented upon completion of a schedule component, the schedule is described as a second order schedule. A more detailed description of the possible permutations of schedules of reinforcement appears in Ferster and Skinner 1957; Kelleher et al., 1975; Spealman and Goldberg 1978; and Spealman et al., 1983.

One critical methodological consideration in studies of human drug self-administration is the difficulty or complexity of the operant performance required for drug acquisition. A variety of types of operant manipulanda have been developed in different laboratories (see Mello and Mendelson 1987 for review). Operant manipulanda vary in terms of the conceptual and physical demands of the required task. On the dimension of physical effort, both strenuous tasks such as riding an exercycle and effortless tasks, such as breaking a photocell beam have been used (Bigelow et al., 1976; Nathan et al., 1970). More conceptually demanding tasks have required performance on a complex matching-to-sample device (Mello 1973) and assembly of a wooden stool (Miles et al. 1974).

In our laboratory, the primary question has usually been to examine spontaneous patterns of drug acquisition and use and their relationship to biological and behavioral variables (Mello and Mendelson 1978, 1987). Consequently, we have used very simple tasks where drug intoxication could not impair performance and thereby compromise drug acquisition. The operant performance of social drug users who do not meet DSM III-r criteria for substance abuse and dependence could be disrupted during intoxication (DSM III-r 1987). However, alcohol-dependent individuals develop behavioral tolerance for alcohol which permits effective performance on quite complex tasks (Mello 1973; Mello and Mendelson 1987).

For the purpose of illustration, operant studies of drug self-administration conducted at the clinical research facility of the Harvard-McLean Alcohol and Drug Abuse Research Center will be described. These clinical studies have involved use of a portable manipulandum shown schematically in figure 1. Each response on the manipulandum transmits a radio-frequency signal on a discrete bandwidth which activates computer-based programming and recording circuitry in an adjacent room. Operant response patterns were automatically recorded by the computer and both the rate of response and inter-response times could be measured.

Subjects were required to press the button on the manipulandum on a time-based schedule, a fixed interval l-second scheduleof reinforcement (FI-1 sec). Only the first response after 1 second elapsed was recorded as an effective response by the programming circuitry. A signal light flashed each time an effective response was made. Subjects could earn one purchase point for 300 effective responses on an FI 1-sec schedule. This schedule is designated as a second-order FR-300 (FI-1 sec:S) and required at least 5 minutes of sustained operant work for each purchase point. The number of purchase points required depended on the specific reinforcer. Although subjects always performed on the same basic schedule of reinforcement, the cost for each drug dose could be varied by changing the number of purchase points required. The prices of different drugs or of money reinforcers could be assigned a purchase point cost which reflected the current prevailing market rates. One advantage of a time-based schedule such as an FI-1 sec schedule, is that the price of a single drug dose can easily be translated into time required at the operant task. For example, a drug that cost three purchase points required 15 minutes of operant work; a drug that cost six purchase points required 30 minutes of operant work.

Subjects were allowed to work on this operant task at any time and a record of their point accumulation was continuously available on a control panel in the Day Room. Whenever a subject elected to purchase a drug, a marijuana cigarette or an alcohol drink, the points spent were immediately deducted from the accumulated reinforcement points. Points earned for drugs and for money were not interchangeable. The total amount of money earned over the course of the study was given to the subject at the end of the study.

We have used this simple procedure to study self-administration of alcohol, marijuana and heroin and the concurrent self-administration of marijuana and alcohol. (Mello et al., 1978, 1981, 1982, 1985, 1989; Mendelson et al., 1976a, b and c; Mendelson and Mello 1988). The manipulandum and the task have been acceptable to volunteer subjects.

They have not been able to tamper with or to destroy this device. Subjects are able to perform the operant task while talking, reading, watching television and eating. Although this manipulandum can be used with virtually any schedule of reinforcement, we have continued to use the FI 1-sec schedule to permit comparisons across successive studies with different types of drugs. This task has been shown to yield reliable data on drug self-administration patterns as well as rates of operant responding.

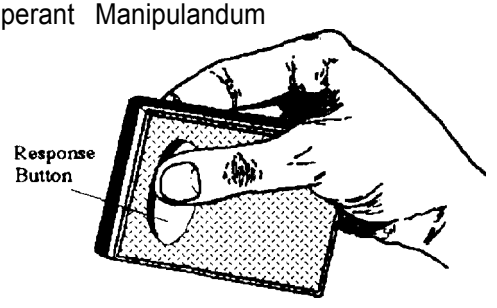

Figure 1: *Portable operant manipulandum used to study heroin, marijuana and alcohol self-administration. Each response transmits a radio frequency signal to the programming circuitry. Reprinted with permission from M. A. Bozarth (ed.), Methods of Assessing the Reinforcing Properties of Abused Drugs. NY: Springer-Verlag, 1987, p. 537.*

OPERANT STUDIES OF ALCOHOL, MARIJUANA AND POLYDRUG SELF-ADMINISTRATION

Selected studies of alcohol, marijuana and concurrent marijuana and alcohol self-administration using the portable operant manipulandum and a second order FR-300 (FI-1 sec:S) schedule of reinforcement are summarized in this section. These studies illustrate the application of operant procedures in clinical research on drug self-administration. In each study described below, volunteer subjects provided Informed Consent and lived on a clinical research ward for several weeks. Subjects were observed during a drug-free baseline, a period of drug self-administration, and a post-drug baseline period. An own-control design is essential for human drug self-administration studies since the use of "normal" drug-naive subjects as a control group in the conventional sense is precluded by both medical and ethical considerations. Behavioral studies were conducted simultaneously with physiological, biochemical, and neuroendocrine studies designed to examine the biological effects of chronic drug use.

Operant Studies of Alcohol Self-Administration

Twenty-six women who were social drinkers worked at a simple operant task for alcohol for 21 days (Mello et al., 1989) and the effects of chronic drinking on menstrual cycle function were concurrently evaluated (Mendelson and Mello 1988). Women could also work for money, a non-drug reinforcer, throughout the 35 day study. Subjects could earn 50¢ or could purchase one drink for six purchase points which required about 30 minutes of work on the operant task. One drink was a 50 ml miniature of distilled spirits, one 12 ounce can of beer or one 12.5 ounce glass of table wine. Five of the 26 women were classified as heavy drinkers and they consumed an average of 7.8 drinks per day. Twelve women were classified as moderate drinkers and they consumed an average of 3.8 drinks per day. Nine women were classified as occasional drinkers and they drank an average of two drinks per day.

Drinking patterns in individual women are shown in figure 2. It is apparent that individual drinking patterns fluctuated markedly from day to day. The heavy and moderate drinker each had more days of peak alcohol consumption than the occasional drinker. The heavy drinker drank more than the moderate drinker on each peak consumption day, i.e., the peaks were of higher amplitude.

In an effort to quantify these individual variations in daily drinking patterns, we used a computerized analysis of pulse-frequency and pulse-amplitude to define the number of daily peaks in alcohol consumption and the interval between successive peaks. Group data were consistent with individual patterns shown in figure 2. The moderate drinkers had more peaks in alcohol consumption (a group average of 6.3) than the heavy drinkers who averaged 5.6 peaks over 21 days. The occasional drinkers had significantly fewer peaks in alcohol consumption than the moderate drinkers and averaged 4.5 peaks. The average number of drinks comprising each peak was significantly greater for the heavy and the moderate drinkers, than for the occasional drinkers and were respectively 6.3, 5, and 2.6 drinks per peak. Although peaks in alcohol consumption occurred more frequently for the moderate and heavy drinkers (every 3.2 and 3.6 days) than for the occasional drinkers (4.6 days), these differences were not statistically significant.

A marked cyclicity in alcohol consumption has been previously observed in clinical research ward studies of alcohol-dependent men where alcohol acquisition was contingent upon performance on an operant behavioral task (Mello and Mendelson 1972; Nathan and O'Brien 1971; Nathan et al., 1970). Alcohol-dependent men often alternated between working for

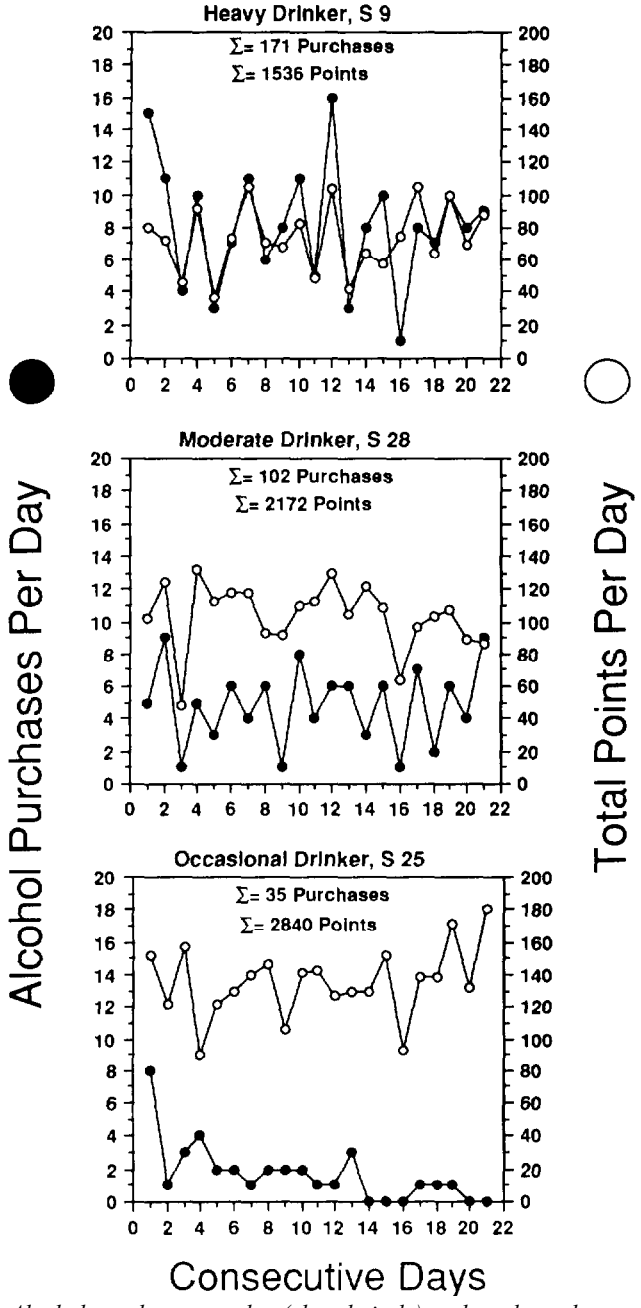

Figure 2: *Alcohol purchases per day (closed circle) and total purchase points earned for both alcohol and money per day (open circle) by an individual heavy, moderate and occasional drinker over 21 days of alcohol availability. The total number of alcohol purchases and the total number ofpurchasepoints earned by each subject are shown at the center top of each graph.*

alcohol for 2 to 3 days and drinking for 2 to 3 days (Mello and Mendelson 1972). These alternate periods of drinking and alcohol abstinent working corresponded to many alcoholics' self-reports of "spree" drinking in the real world. The abrupt cessation of drinking and accompanying rapid fall in blood alcohol levels were often associated with alcohol withdrawal signs and symptoms. A marked cyclicity in alcohol administration has also been seen in alcohol self-administration studies in a primate model using both an intravenous (Winger and Woods 1973; Woods et al., 1971) and an intragastric (Altshuler and Tally 1977) route of alcohol administration (see Mello 1979 for review). In contrast, figure 2 shows that days of maximal drinking were significantly correlated with days of maximal operant work in female social drinkers. Alcohol did not impair operant performance in heavy, moderate or occasional social drinkers (Mello et al., 1989).

Operant Studies of Marijuana Self-Administration

A number of studies of operant work-contingent acquisition of marijuana have been conducted to evaluate the effects of marijuana on behavior and physiological parameters (Mendelson et al., 1974, 1976; Miles et al., 1974; Mello and Mendelson 1985). The behavioral effects often ascribed to marijuana include apathy, lethargy, diminished "drive" and ambition, decreased productivity and goal directedness, and indolence. Clinical evidence suggests that these apparent motivational impairments may reflect problems unrelated to marijuana use (Kolansky and Moore 1972; Negrete 1983, Halikas 1974). The hypothesis that marijuana induces an "amotivational" syndrome has persisted despite the lack of supporting evidence in behavioral studies.

In each study where marijuana availability was contingent upon performance of an operant task, subjects worked far longer than was required to earn the marijuana smoked and usually accumulated points for money. In one of the early studies, subjects were limited to earning a maximumof 60,000 points on a Fixed Ratio schedule each day (Mendelson et al., 1974). In that study, subjects consistently earned the maximum number of points available and showed no evidence of a marijuana-induced impairment in work and/or motivation (Mendelson et al., 1974). In subsequent studies, subjects were given unlimited access to marijuana for 21 days contingent upon operant task performance under controlled research ward conditions. When subjects could earn a 1 gram marijuana cigarette (or 50¢) by 30 minutes of sustained performance on a simple operant task, both men and women worked far more hours each day than was necessary to earn the number of marijuana cigarettes they smoked (Mendelson et al., 1976b; Mello and Mendelson 1985). Subjects contin-

ued to perform the operant task after smoking 10 or more marijuana cigarettes per day. Women showed no marijuana dose-related effects on operant performance (Mello and Mendelson 1985). The heavy, moderate and occasional marijuana smokers smoked an average of 6.1 (±1.45), 2.72 (±0.16) and 0.90 (±0.22) marijuana cigarettes per day. These three groups did not differ in operant purchase points earned, hours worked or money earned. Some womencontinued to workformoney while smoking 15 to 20 marijuana cigarettes per day and the period of maximal operant work coincided with the periods of maximal marijuana smoking (noon to midnight) (Mello and Mendelson 1985). Illustrative data for women who were heavy marijuana smokers are shown in figure 3. The concordance between marijuana smoking and operant performance is similar to data shown in figure 2 for social drinkers.

A lack of significant effects of high doses of marijuana on performance is consistent across studies in men and women (Lessin and Thomas 1976; Mendelson et al., 1974, 1976; Mello et al., 1978; Mello and Mendelson 1985; Miles et al., 1974). The hypothesis that marijuana induces an "amotivational syndrome" wouldpredictthatmarijuana availability would decrease operant performance and that subjects would not work for money during marijuana intoxication. Consequently, these data are not compatible with the hypothesis that marijuana smoking produces an "amotivational" syndrome, since subjects continued to work for money, a conventional reinforcer, as well as for marijuana even during heavy marijuana smoking.

Moreover, heavy marijuana users tended to increase marijuana smoking during a 21 day period of marijuana availability (Mendelson et al., 1976; Mello and Mendelson 1985). The major difference between men and women studied under comparable conditions was that all men increased marijuana smoking over time (Mendelson et al., 1976), whereas the female moderate and occasional marijuana smokers either decreased marijuana smoking or maintained a relatively stable pattern of marijuana use across the 21 days of marijuana availability (Mello and Mendelson 1985).

Operant Studies of Concurrent Marijuana and Alcohol Self-Administration

Probably the most effective way in which continuous access drug self-administration procedures can be used to compare the relative reinforcing properties of drugs is when two or more drugs are concurrently available, contingent upon operant performance. There have been relatively few such studies and the primary behavioral question has usually been to determine if the simultaneous availability of two drugs, such as

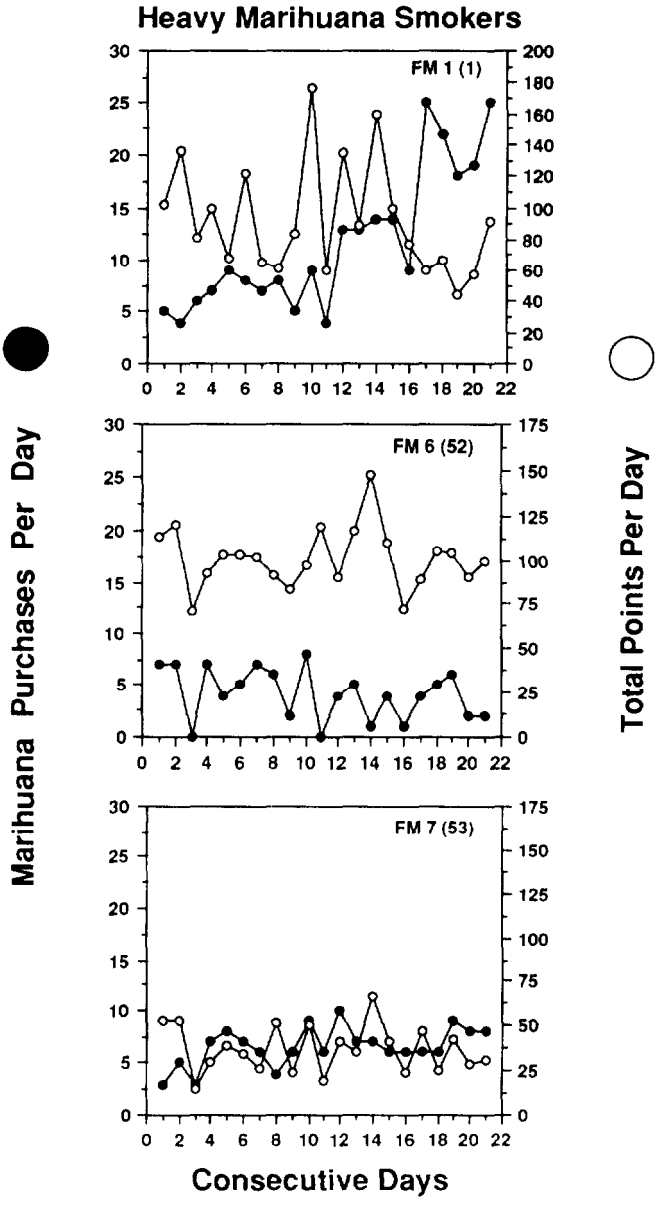

Figure 3: *Daily patterns of marijuana purchases and total points earned by three women classified as heavy marijuana smokers. The number of 1 gram marijuana cigarettes, (1.8 to 2.3 percent Δ^9-THC) purchased each day are shown as closed circles. The total number of points earned for marijuana and for money each day are shown as open circles. The total number of marijuana cigarettes purchased and the total number of points earned during the 21 days of marijuana availability are shown at the top of each figure. These data were adapted from Mello and Mendelson 1985.*

marijuana and alcohol, will result in a significant increase or decrease in the use of one or both drugs (Mello et al., 1978). Patterns of drug use during 10 days of concurrent access to marijuana and alcohol were compared with consecutive 5 day periods when only *alcohol* or *only marijuana* were available. Sixteen male volunteers with a history of concurrent alcohol and marijuana use lived on a clinical research ward for 34 consecutive days. Subjects could earn money (50¢) or marijuana (a 1 g cigarette; 1.8-2.3 percent Δ^9-THC) by working at the simple operant task on a Fixed Interval 1 sec schedule of reinforcement for 30 minutes. Alcohol (30 ml) was available as wine, beer, or distilled spirits for 15 minutes of operant work.

Fourteen of the 16 subjects drank less alcohol when marijuana was concurrently available and alcohol consumption remained depressed throughout the 10 day period. Seven of the 14 subjects drank significantly less alcohol during concurrent marijuana availability than when only alcohol was available ($P < .05$-$.001$). Figure 4 shows average alcohol and marijuana consumption by four heavy drinkers. Twelve subjects smoked slightly more marijuana when alcohol was available but the magnitude of this increase was not significant in ten instances. Only two subjects increased use of both alcohol and marijuana during concurrent alcohol and marijuana availability. Although alcohol and marijuana were usually used together, there were no instances of adverse reactions or other evidence of toxic drug interactions.

These data are not consistent with the notion that the simultaneous availability of marijuana and alcohol will lead to a significant increase in the use of both drugs. Rather, alcohol consumption decreased when marijuana was available and marijuana use tended to increase through time independently of concurrent alcohol availability (Mello et al., 1978). Subsequent studies of the acute effects of concurrent alcohol and marijuana use suggest that pre-treatment with marijuana may delay gastric emptying and therefore delay alcohol absorption and intoxication (Lukas unpublished observations).

Tobacco Smoking During Other Drug Use: The question of how the availability of one drug affects the concurrent use of another drug has most often been asked in connection with tobacco smoking during other drug self-administration (see Mello and Mendelson 1986 for review). In most instances, tobacco was freely available rather than contingent upon performance of an operant task. Tobacco cigarette smoking usually increases during intoxication with alcohol, opiates, and certain stimulants (Mello and Mendelson 1986). Increased tobacco smoking during

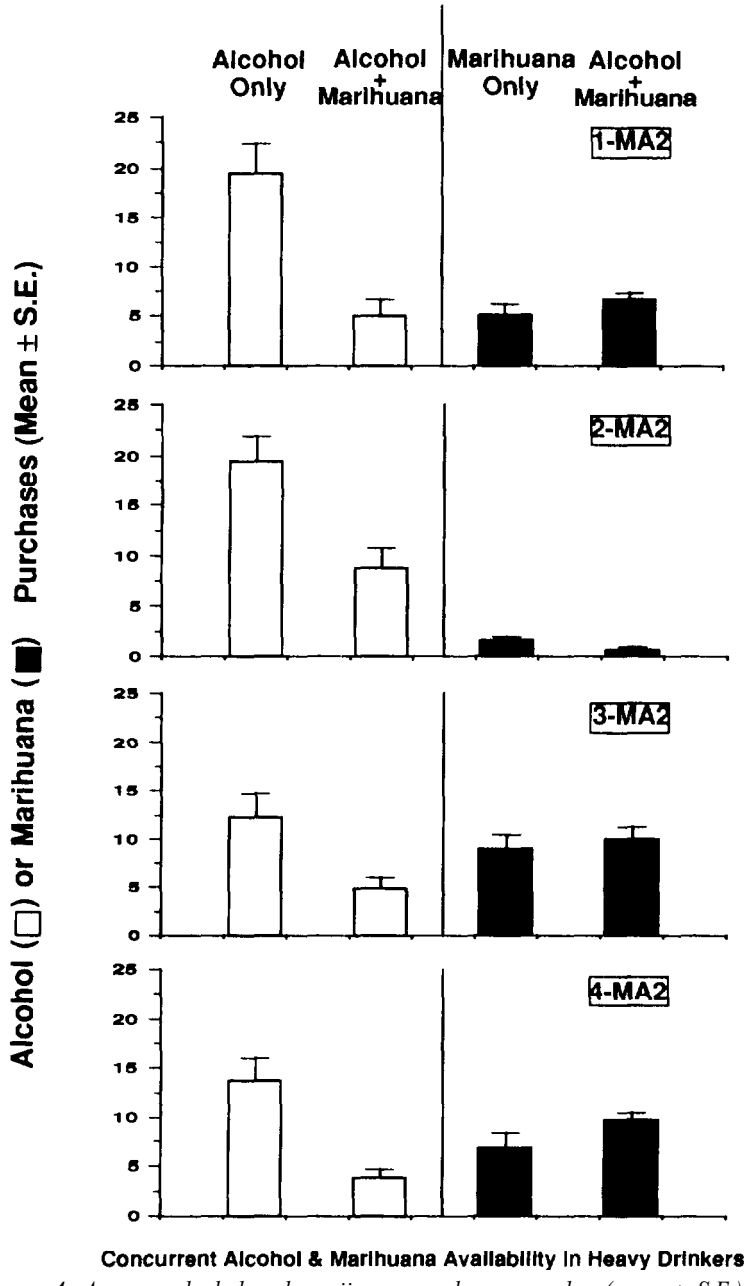

Figure 4: *Average alcohol and marijuana purchases per day (mean ± S.E.) by four individual subjects. Columns 1 and 2 show alcohol purchases when only alcohol was available and when both alcohol and marijuana were available. Columns 3 and 4 show marijuana cigarette purchases when only marijuana was available and when alcohol and marijuana were concurrently available. These data were adapted from Mello et al.. 1978, table 1.*

other drug intoxication has been consistently observed in studies using different experimental paradigms. These findings are summarized schematically in figure 5.

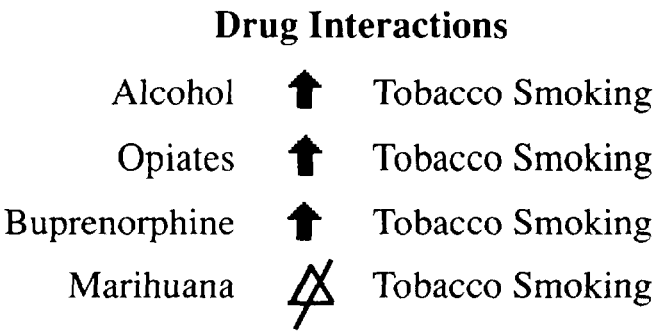

Figure 5.

The interactions between tobacco smoking and alcohol consumption have been most frequently studied. It has been consistently observed that alcohol consumption is associated with increased cigarette smoking in social drinkers as well as in alcohol-dependent individuals (Griffiths et al., 1976; Mello et al., 1978, 1987; Henningfield et al., 1983, 1984; see Mello and Mendelson 1986 for review), In social drinkers, both daily alcohol consumption and administration of a single dose of alcohol appear to facilitate cigarette smoking (Mello et., 1980a, 1987; Henningfield et al., 1984).

Heroin and methadone intoxication also are associated with increased cigarette smoking by opiate addicts (Mello et al., 1980b, Chait and Griffiths 1984). Moreover, a gradual decrease in daily methadone maintenance dose was associated with decreased cigarette smoking (Bigelow et al., 198 1). Administration of buprenorphine, an opioid mixed agonist-antagonist, was also accompanied by significantly increased cigarette smoking in heroin addicts (Mello et al., 1985) whereas opiate antagonists, such as naltrexone and naloxone, had no effect on total cigarettes smoked or on smoking-related measures, including carbon monoxide levels in expired air across the naloxone dose range studied (Mello et al., 1980b; Nemeth-Coslett and Griffiths 1986).

In contrast to alcohol, opiates and certain stimulants, marijuana does not appear to alter tobacco smoking in any systematic way (Mello and Mendelson 1985; Nemeth-Coslett et al., 1986). Pre-treatment with a single marijuana cigarette did not significantly change cigarette smoking by volunteer subjects (Nemeth-Coslett et al., 1986). Cigarette smoking

during 21 days of operant work-contingent marijuana smoking was examined in 16 women (Mello and Mendelson 1985). Cigarettes were freely available upon request throughout the study. The amount and temporal pattern of tobacco cigarette smoking during drug-free conditions did not change during concurrent marijuana use by either heavy or moderate marijuana smokers (Mello and Mendelson 1985). Although it might be expected that marijuana smoking and tobacco smoking would be antithetical, both drugs were usually smoked in close temporal contiguity (Mello and Mendelson 1985). Concurrent studies of pulmonary function indicated that single breath carbon monoxide diffusion capacity was significantly lower in female marijuana smokers than in tobacco cigarette smokers and non-smoker control subjects (Tilles et al, 1985).

The facilitator-y effect of alcohol, opioid agonists, opioid mixed agonist-antagonists (Mello and Mendelson 1986) and some stimulants (Schuster et al., 1979; Henningfield and Griffiths 1981) on cigarette smoking is difficult to explain. Since these drugs have a broad spectrum of actions, it is difficult to construct a plausible hypothesis concerning specific pharmacological effects on cigarette smoking. These data illustrate the difficulty in adequately specifying the nature of the reinforcer in polydrug use. Simultaneous use of drugs which appear to have contradictory pharmacological effects is especially puzzling (Mello 1983). Since multiple drug use appears to be an increasingly common pattern (Kreek 1987, 1989), the way in which drugs interact to modulate use patterns is an important area for further study.

ISSUES IN THE PREDICTION OF DRUG ABUSE LIABILITY IN HUMANS

Clinical research on spontaneous drug use patterns and assessment of drug effects during intoxication has shown that the behavioral effects of drugs are very complex. Figure 6 graphically depicts some of the reported "positive" and "negative" effects of intoxication with alcohol, marijuana, opiates, and other abused substances. If drug intoxication were consistently associated with "positive" consequences and these effects could be clearly described, then the prediction of the abuse liability of new drugs might be relatively simple. If a test drug produced more "positive" than "negative" effects, would this necessarily predict drug abuse liability? The answer is a qualified no. Chronic intoxication with alcohol and heroin is often associated with increased dysphoria and anxiety rather than with alleviation of depression or induction of tranquility or elation (see Mello 1983 for review).

One of the most perplexing aspects of chronic alcohol and opiate abuse is the discordance between the commonly anticipated and observed changes in reports of subjective states (see Mello 1983 for review). Several studies have shown that alcohol-dependent men tend to recall their anticipated positive reactions to alcohol rather than the depression, anxiety and lowered self-esteem consistently observed during alcohol intoxication. Clinical studies further suggest that alcohol-dependent men have a very clear recollection of their first drink, but the first drink was memorable because it was associated with intoxication and attendant nausea, vomiting and despondency, not with positive feelings. Similarly, the acute effects of opiates, barbiturates, and nicotine in naive users may be associated with nausea, vomiting, anxiety and other adverse effects which could not be considered positive or pleasurable in the usual sense (Mello 1983). Some opiate abusers report a more positive initial reaction to opiates and other abused drugs, but these findings are the exception (Haertzen et al., 1983). Yet, it is obvious that drug use continues despite the initial aversive consequences and despite the many adverse consequences of chronic intoxication.

One implication of data on the dysphoric effects of drug intoxication is that there is no simple formula for the prediction of drug abuse liability. Mild to severe negative consequences of drug intoxication do not necessarily preclude drug abuse. Phencyclidine abuse is one compelling example which illustrates that psychotic reactions, stupor, and life-threatening coma may not deter the phencyclidine abuser (Mello 1978). Conversely, a preponderance of "positive" effects of drug intoxication may not necessarily ensure abuse liability. It is difficult to think of an example of a drug that induces only positive effects.

In contrast to chronic use, acute drug intoxication often may be associated with primarily positive effects. Transient positive changes in mood often occur during the rising phase of the plasma drug concentration curve. Opiates and cocaine may produce positive changes in feeling state within seconds or minutes following intravenous administration. Alcohol may produce positive mood changes within 30 to 90 minutes after drinking, during the rising phase of the blood alcohol curve. Positive mood changes are often associated with transient increases in electroencephalogram (EEG) alpha activity (Lukas et al., 1987). However, during the falling phase of the drug concentration curve, negative and dysphoric changes in feeling state may occur. The falling phase of the blood alcohol curve may be associated with increased anxiety and dysphoria. The dysphoric crash after the cocaine "high" is more dramatic, but similar. It appears that the negative effects of chronic intoxication are reflected in microcosm in the falling phase of the plasma drug concentration (Mello 1983).

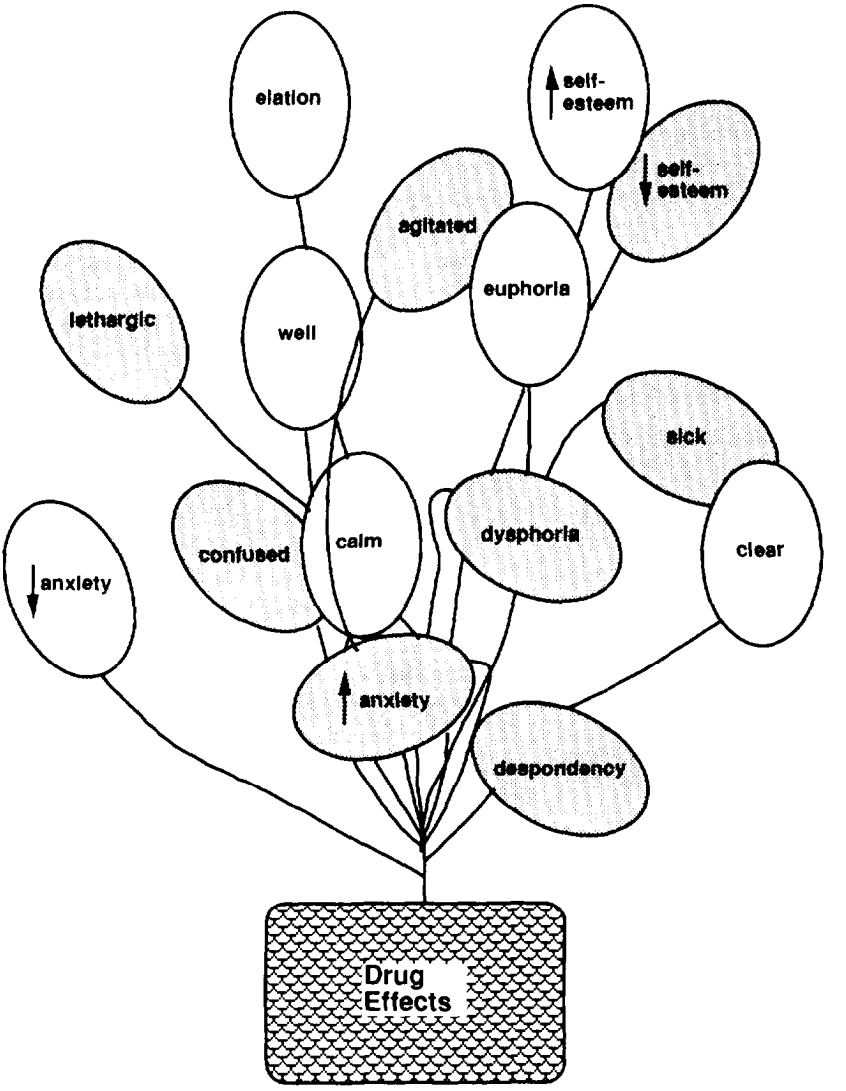

Figure 6: *A schematic diagram illustrating the disparate effects of drug* intoxication *reported by naive and experienced drug users (see Mello 1983).*

The seemingly paradoxical findings summarized schematically in figure 6 prompt the hypothesis that the aversive consequences of drug intoxication are one important component of the total reinforcing complex. To minimize or dismiss these clinical data is to ignore an important behavioral consequence of drug intoxication. Moreover, there is considerable evidence from basic behavioral science that seemingly aversive events can maintain behavior leading to their repeated administration (see Mello 1983; Spealman et al., 1983 for review). Aversive stimuli such as electric shock can maintain response behavior leading to shock administration. Response-produced shock illustrates an important principle that the same stimulus event may have either reinforcing or punishing effects depending on the conditions under which it is presented. The parallels between these models of aversive control of behavior and the dysphoric effects of drug intoxication are provocative. It is possible that the seemingly aversive component of drug intoxication also may be reinforcing under certain conditions. As indicated in figure 6, a reinforcer is any event that maintains behavior leading to its administration. Reinforcement is a neutral term with no inherent "positive" or "negative" connotations. Meaningful analysis of the way in whichdrugs serve as reinforcers andcontrol behavior leading to their self-administration requires examination of all the discernible behavioral consequences. Any or all of these consequences may be reinforcing and may contribute to drug abuse liability. Systematic study of the relationship between the behavioral effects of drug intoxication and subsequent drug use may eventually clarify this issue. Verbal behavior is often minimally correlated with behavior, and drug users inaccurately recall the effects of drugs during intoxication. Consequently, rather than relying upon recall during sobriety, there is no substitute for *direct observation of drug self-administration behavior,* and there is no adequate alternative to evaluating *drug effects during intoxication.*

The prediction of drug abuse liability is even further complicated by polydrug use. Simultaneous use of drugs with contradictory pharmacologic effects such as cocaine and heroin or cocaine and alcohol further challenges any simplistic hypothesis about optimal drug effects. It is possible that any drug or drug combination that has definite stimulus properties and behavioral effects may have abuse potential. Clinical data on the dysphoric effects of drugs and accounts of polydrug use which involve concurrent use of, for example, stimulants and depressants have prompted the speculation that a change in state per se may be the critical reinforcing component of drug intoxication. The direction of that change in state, *up* or *down,* may be far less important than the change itself. Insofar as drugs are stimuli leading to some change in subjective state, it may be useful to think of drug self-administration as a form of stimulus

self-administration (Mello 1977, 1978, 1983). This hypothesis implies that any drug which has definite stimulus properties, that is, behavioral effects for the user, is a drug which has abuse potential. Once we achieve a better understanding of the behavioral consequences of drug intoxication and the factors that maintain drug use and abuse, procedures for predicting abuse liability as well as procedures for treatment intervention should be more effective.

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CHAPTER 9

The Use of Choice Procedures for Assessing the Reinforcing Properties of Drugs in Humans'

Chris E. Johanson, Ph.D.
Harriet de Wit, Ph.D.

INTRODUCTION

This presentation will review a series of studies that were conducted at the University of Chicago beginning in 1978 on the reinforcing properties of psychomotor stimulants, benzodiazepines, and alcohol in humans using a preference procedure. These studies were conducted in collaboration with several other investigators including E.H. Uhlenhuth, L. Chait, and S. McCracken but they owe their initiation and continuation to the encouragement of Charles R. Schuster. The initial purpose of these human self-administration studies was to validate a choice methodology that our group developed for use with rhesus monkeys. The procedure with animals was designed to evaluate the relative reinforcing properties of drugs as a means of more accurately predicting dependence potential (e.g., Johanson and Schuster 1975; Johanson 1975). The validity of these predictions was hard to evaluate because of the difficulties of obtaining accurate survey data, such as that provided by the Drug Abuse Warning Network (DAWN). However, if studies performed with normal human volunteers using a choice, or preference procedure yielded predictions that were comparable to those obtained with rhesus monkeys, this might indicate that the approach of using animals was at least as useful for predicting dependence potential as human studies (see Johanson et al., 1987, for a discussion of validity issues). In addition to the desire to validate animal models, there was renewed interest at that time in developing new approaches using humans for the prediction of dependence potential. This renewed interest was in part due to the legal changes which had occurred in the mid-1970s that prohibited the use of prisoner

[1] The opinions expressed are those of the authors and do not necessarily reflect the views of the Department of Defense of the Uniformed Services University of Health Sciences.

volunteers as experimental subjects at the Addiction Research Center (ARC) in Lexington, KY. This history is reviewed by Jaffe and Jaffe (this volume).

It is important to state explicitly a major assumption of the studies to be described. The assumption derives from the results of animal studies which have shown that the drugs which animals self-administer, or which function as positive reinforcers, are the same drugs that humans abuse (Johanson and Balster 1978). Likewise, drugs which are not self-administered, such as chlorpromazine, are drugs which are not considered drugs of abuse for humans. Although there are exceptions in both directions, the correlation between predictions that could be made on the basis of results from animal studies and the actual abuse of drugs by humans is so good that results from animal drug self-administration studies are routinely used for making drug scheduling decisions at the international level. This assumption of a direct relationship between reinforcing properties and dependence potential was used as a basis for our human choice studies. The assumption was broadened in subsequent studies designed to assess risk factors predisposing certain individuals to abuse a drug to include the notion that in order for a drug to be abused by an individual, it must initially function as a reinforcer. All else being equal, a human who finds a drug reinforcing will be more likely to abuse that drug than an individual who does not. However, this condition of drug reinforcement is necessary but not sufficient, since other factors (e.g., availability, peer pressure, punishment, cost) subsequently influence the likelihood that an individual begins abusing a drug. Interestingly, many of these other factors can be studied experimentally in humans as well as animals but, to date, few studies have been attempted (e.g., Johanson 1977; Griffiths et al, 1974).

Although the major aim of the research was to simulate procedures used in animals, an additional component of the design was to concurrently measure actual drug-taking behavior, or self-administration, and subjective drug effects. Previous studies in humans that had been conducted at the ARC focused on evaluating the physiological and subjective effects of drugs in drug-experienced participants. Martin, Jasinski and their colleagues had published an extensive series of studies on the physiological and subjective effects of classic drugs of abuse such as the opiates (Jasinski 1973; Jasinski et al. 1968, 1970; Martin et al. 1973), the amphetamines (Jasinski et al. 1974; Martin et al. 1971; Martin 1973), and sedatives (Jasinski 1973). The purpose of their investigations had been to provide a complete pharmacological profile of these drugs to be used as standards of comparison. Further, it was assumed that these profiles of action were clues to understanding the mechanisms responsible for their abuse. The

extent to which other drugs shared characteristics provided a basis for predicting their dependence potential as well as mechanism of action. However, these studies had not attempted to correlate subjective and physiological effects with actual drug-taking. Thus, in order to determine their correspondence, we combined the approach used at the ARC of measuring subjective effects with the approach in animals of assessing self-administration behavior.

There are several ways in which the experimental design that has been used in these preference studies can be distinguished from the approach used by other investigators such as Roache and Griffiths (this volume) and Fischman (this volume). First, normal human volunteers, rather than present or past drug abusers were recruited for participation. Using this type of population allows an estimate of the dependence potential of a drug in initial drug users rather than in populations that have already demonstrated a propensity for abusing drugs of a particular type. As will be seen when subsequent studies are described, the use of normal human volunteers allows certain types of experimental questions to be addressed that could not be evaluated in participants who were already experienced drug users. Conversely, there are experimental questions that cannot be addressed using volunteers without extensive drug experience.

A second major difference in the experimental protocol was that for the majority of studies, particularly the ones conducted initially, participants did not remain in a laboratory environment after drug ingestion. Because participants were allowed to leave, it was also necessary to use low and infrequent doses of drugs. Allowing participants to return to their normal day-today activities has probably had a major impact on the results and it is possible that such results, generated outside the constraints of a laboratory, may be more generalizable to naturalistic conditions. However, it is also important to compare results across environmental conditions to determine the importance of this variable, particularly since it is not feasible to test certain classes of drugs outside the laboratory.

INITIAL STUDIES

We begin this review by describing in detail the first two experiments that were conducted in order to illustrate the general methodology (Johanson and Uhlenhuth 1980a,b). In addition, the results generated by these two initial experiments formed the basis for two series of subsequent studies that investigated the influence of different classes of variables on the reinforcing properties of stimulants and depressants.

One of the initial studies (Johanson and Uhlenhuth 1980a) was designed to determine whether normal human volunteers would self-administer 5 mg d-amphetamine, a drug which has been shown in animal studies to function as a positive reinforcer (Balster and Schuster 1973). The second study evaluated the reinforcing properties of several doses of diazepam (Johanson and Uhlenhuth 1980b). The reinforcing properties of this drug have also been tested in animals. Although responding can be maintained by this drug, the reinforcing properties of benzodiazepines in general are not robust (Bergman and Johanson 1985; Ator and Griffiths 1987). Therefore, by selecting two drugs that might lead to different results, the specificity of the procedure could be evaluated.

Participants

The participants in the amphetamine experiment were 3 1 normal human volunteers (10 female and 21 male) between the ages of 21 and 32. Ten of these individuals also participated in the diazepam study. Candidates were only accepted if they were considered normal and in good health, based upon interviews and a physical examination, and were excluded if they had any history of drug-related problems. The experimental protocol was approved by the local institutional review board and participants signed an informed consent which described the study in detail and indicated all possible side effects across several drug classes. Each participant agreed not to take other drugs except their normal amounts of coffee and cigarettes 12 hr before and 6 hr after receiving drug. Volunteers were paid for their participation.

Procedure

Each experiment consisted of three sessions per week over a 3-week period for a total of nine sessions. During the first four sessions, the participant reported to the experimental room in the morning. At that time, he/she filled out mood forms that will be described later and received a colored capsule for immediate ingestion. Approximately half of the participants received drug during sessions 1 and 3 and placebo during sessions 2 and 4. The order was reversed for the other half. For each participant, each drug was dispensed in a capsule of a consistent and distinctive color in order to facilitate identification. Capsule colors were assigned randomly across participants to avoid the influence of color preference. Each participant was instructed during the initial four sessions to note the capsule colors and to try to associate each of the two colors with the effects of the substances contained in them. After ingesting the capsule, participants were free to leave. They took three additional sets

of mood forms with them, which they were to fill out 1, 3, and 6 hrs later. During the last five sessions, the procedure was identical in every respect except that the participants weregiven a choice of the two colored capsules to ingest.

The amphetamine preference study consisted of a single 3-week experiment comparing 5 mg *d*-amphetamine to placebo. In the diazepam study, three separate experiments were conducted, in counterbalanced order, comparing three doses of diazepam (2, 5, and 10 mg) to placebo. The measure of preference, or choice, was the percentage of sessions that active drug was selected. In the initial studies, these choice results were analyzed using a two-tailed *t*-test, which assumes that by chance, participants will choose one color on 50 percent of the choice sessions. In later studies, a log-linear analysis was used because the 50 percent assumption did not appear to be valid. Only significant results ($p<.05$) will be described unless otherwise stated.

Subjective Effects: The only questionnaire that was used to assess mood in the initial studies was an experimental version of the Profile of Mood States (POMS; McNair et al., 1971). Thisversion consists of 72 adjectives commonly used to describe momentary mood states. Participants indicate how they feel at the moment in relation to each adjective on a 5-point scale from "not at all" (0) to "extremely" (4). There are eight clusters of adjectives which have been grouped using factor analysis. These clusters, or scales, have been given names that reflect the adjectives includedin the cluster (Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation). The value of each scale is determined by adding the numbers checked for each adjective and dividing the total by the number of adjectives in that cluster. Two additional scales (unvalidated) were derived from other scales: Arousal = (Anxiety + Vigor) — (Fatigue + Confusion); Positive Mood = Elation — Depression.

The scores of the POMS scales were averaged for each participant at each time period (prior to ingestion [0] and 1, 3, and 6 hrs post-ingestion) separately across drug sessions and across placebo sessions. If a significant ($p < 0.05$) drug x hour interaction was found, further statistical tests were conducted to determine at which hours the scores for drug and placebo were significantly different. In some cases, the subjective effects were averaged across the entire 9-session experiment whereas in other studies, only data from the sampling sessions were used in order to avoid possible confounding because of expectancies. Unless specified otherwise, only significantresults will be discussed and it should be assumed that changes are described in relationship to placebo scores.

In subsequent studies, many additional questionnaires (e.g., Addiction Research Center Inventory (ARCI), visual analog scales, measures of liking, drug identification) were used to assess subjective effects. In general, these questionnaires were analyzed like the POMS although in some cases, *t*-tests and x^2 analyses were more appropriate. These additional measures have been extremely important in assessing reliability of the evaluation of subjective effects by providing verification across instruments of a specific change in mood (e.g., Anxiety scale of the POMS and "anxiety" as measured by a visual analog scale). However, the results from these other mood scales will only occasionally be reported and the reader is referred to the original publications.

Results

Figures 1 and 2 show the results of the amphetamine and diazepam studies. Amphetamine in this experiment was chosen an average of four out of five opportunities. In contrast, 2 mg diazepam was chosen at chance level whereas at the higher doses of 5 and 10 mg, participants preferred the capsule containing placebo. However, one of the participants preferred both 5 and 10 mg diazepam over placebo on all five choice sessions. In additional experiments conducted with this participant, he chose 5 mg diazepam over both 5 and 10 mg *d*-amphetamine on four of the five choice sessions (data not shown). Thus, while the majority of participants did not choose to self-administer diazepam, there may be individuals who do prefer diazepam. As will be reviewed a little later, subsequent studies with diazepam have attempted to determine whether such individual differences are related to other variables or are predictable.

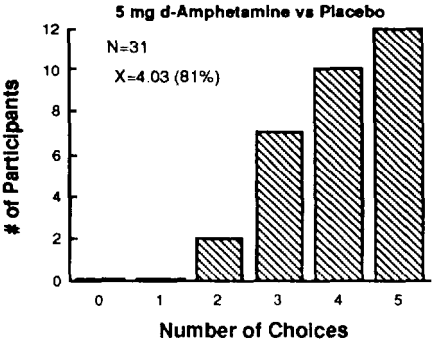

Figure 1: *The number of participants (ordinate) who chose 5 mg d-amphetamine 0 to 5 times (abscissa) during the 5 choice sessions (Johanson and Uhlenhuth 1980a).*

The subjective effects of amphetamine and diazepam were typical of stimulants and depressants and the results indicated that the POMS was a reliable and sensitive instrument for detecting mood changes of relatively low doses and in a situation where the participants were not confined to

a laboratory environment. Amphetamine produced increases in Vigor, Elation, Friendliness, Arousal, and Positive Mood and decreases in Confusion. These effects were time-related, peaking at the 3 hr evaluation. In the 2 mg diazepam experiment, there were no significant changes in the POMS. In the experiments comparing the two higher doses of diazepam to placebo, diazepam produced dose-dependent decreases in Vigor and Arousal and increases in Confusion and Fatigue. These effects were most pronounced after 1 hr and had disappeared after 3 hr for the 5 mg dose and after 6 hr for the 10 mg dose.

In summary, the initial two studies indicated that amphetamine was self-administered whereas in the same population, diazepam did not function as a reinforcer. These results were similar to those found in animal studies. In addition, there was a logical relationship between choice behavior and subjective effects. Amphetamine produced changes in mood that could be interpreted as positive (e.g., increases in Elation and Positive Mood) whereas diazepam did not. Methodologically, these studies indicated that the experimental design was feasible to use and that the instrument measuring mood effects was sensitive to differences in dose, time course, and type of drug. This was particularly striking given the low doses that had been used and lack of control over participants' activities.

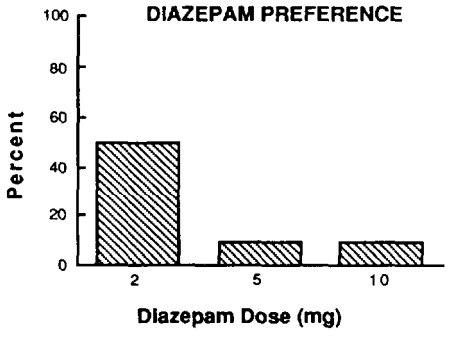

Figure 2: *The percent of participants (ordinate) who chose diazepam during the five choice sessions as a function of diazepam dose.*

REINFORCING PROPERTIES OF PSYCHOMOTOR STIMULANTS

The results obtained with amphetamine, indicating that it functioned as a positive reinforcer in normal volunteers even at a relatively low dose, stimulated a series of studies that sought to investigate the reinforcing properties of other psychomotor stimulant drugs (Johanson and Uhlenhuth 1978; 1982; Chait et al. 1987, 1988; Stem et al., 1989). This series of studies illustrates one of the uses of the choice methodology, i.e., to compare the reinforcing properties of a group of pharmacologically related

drugs. The assumption, as in the previous studies, is that such reinforcing properties are a reflection of the dependence potential of these compounds. This use of the choice methodology is reminiscent of the approach used by the ARC of comparing the profile of different drugs within a pharmacological class on a series of measures including subjective and physiological ones (e.g., Martin et al., 1971). In the present case, however, the comparison is made in terms of preference and profile of subjective effects.

Seven stimulants as well as a higher dose of d-amphetamine have been evaluated using the procedure described above in which number of choices was used as the measure of reinforcing properties. All the drugs except caffeine are marketed as anorectic agents but they differ in terms of their purported central mechanism of action. These studies paralleled self-administration studies in rhesus monkeys conducted concurrently at the University of Chicago that evaluated the reinforcing properties of many of these same drugs (Corwin et al. 1987; Woolverton et al., 1986; Johanson and Schuster 1977). Table 1 lists the results across drugs and doses and shows that amphetamine, benzphetamine, diethylpropion, and phenmetrazine were preferred over placebo. Where more than one dose was evaluated, there did not appear to be any dose-dependent effect. In contrast, caffeine, fenfluramine and phenylpropanolamine (PPA) were not preferred whereas mazindol was clearly avoided. In general, these results paralleled those obtained with rhesus monkeys with the noteworthy exception that mazindol maintains responding in rhesus monkeys (Wilson and Schuster 1976; Corwin et al., 1987) but appeared to have aversive properties in humans in the present study. It remains to be determined whether this difference is due to route of administration (the monkey studies used an intravenous route whereas drug was administered orally in the human studies), species, or other procedural differences. The results obtained in the discriminative stimulus studies (seebelow) indicate that it is not likely that route of administration can account for the discrepancy.

In addition to the differences in preference, there were also differences in subjective effects across drugs. Although a variety of measures of subjective effects have been used, particularly in the most recent studies (e.g., Chait et., 1987), many of these (e.g., ARCI, VAS) have not been used consistently across all studies. Therefore, the comparison will be restricted to the POMS. A liking measure, which was obtained using a 100 mm visual analog scale, is also reported for those drugs for which it was used because of the face validity of this question (see Fischman, this volume). Finally, because different participants were used in each study, an attempt to make quantitative comparisons does not appear justified so

Table 1: Preference for psychomotor stimulants in humans

Drug (mg)	Percent Choice	Reference
5 mg Amphetamine	81	Johanson & Uhlenhuth 1980a
10 mg Amphetamine	78	Johanson et al., 1983
25 mg Benzphetamine	65	Chait et al., 1987
50 mg Benzphetamine	71	Chait et al., 1987
25 mg Diethylpropion	63	Johanson & Uhlenhuth 1978
25 mg Phenmetrazine	63	Chait et al., 1987
50 mg Phenmetrazine	63	Chait et al., 1987
100 mg Caffeine	43	Stem et al., 1989
300 mg Caffeine	39	Stem et al., 1989
20 mg Fenfluramine	50	Johanson & Uhlenhuth 1982
12mg PPA	43	Chait et al., 1987
25 mg PPA	38	Chait et al., 1987
50mg PPA	42	Chait et al., 1987
75 mg PPA	39	Chait et al., 1988
0.5 mg Mazindol	13	Chait et al., 1987
1 mg Mazindol	13	Chait et al., 1987
2 mg Mazindol	12	Chait et al., 1987

that only qualitative results (i.e., whether a drug produced a significant drug by hour interaction) will be reported.

As shown in table 2, the drugs that were preferred over placebo had similar subjective effects. In particular, increases in Arousal and higher liking scores characterized the drugs that were preferred, whereas the remaining drugs either showed no significant subjective effects (e.g., fenfluramine) or only produced increases in POMS Anxiety. However, increases in Anxiety were also seen with amphetamine and phenmetrazine.

The correspondence between choice and subjective effects has also been demonstrated by comparing the subjective effects produced by amphetamine in participants who consistently chose amphetamine

Table 2: Subjective effects of psychomotor stimulants[2,3]

POMS	AMP	BENZ	DEP[4]	PMT	CAF	FFL	PPA	MAZ
Anxiety	+			+	+		+	+
Vigor	+	+		+				
Fatigue	—	—			—			
Friendliness	+	+						
Elation	+							
Arousal	+	+	+	+				
Positive Mood	+							
Liking[5]	Yes	Yes	NE	Yes	NE	No	No	No

(choosers) with those that consistently chose placebo (non-choosers). This type of comparison was originally made using the results from the initial study (Johanson and Uhlenhuth 1980a). Perhaps due to the fact that none of the 31 participants in that study chose placebo more than three times out of five, no significant differences in subjective effects were reported between 2-3 time choosers, 4 time choosers and 5 time choosers. However, a follow-up study that included additional participants (N=45, Uhlenhuth et al, 1981) reported sufficiently intriguing predrug differences in POMS scores that a further analysis, using a different group of participants, was conducted. The explicit purpose of this analysis was to determine whether there were preexisting differences between individuals that predicted preference (de Wit et al., 1986a). In that context,

[2]Table entries are based upon whether a significant drug by hour interaction was obtained on the ANOVA. Only scales for which one of the drugs produced a significant effect are included. A "+" indicates that drug produced an increase relative to placebo and "-" indicates a decrease. Results are reported for the highest dose or overall drug for those drugs reported in Chait et al., 1987. See table 1 for dose(s) and reference.

[3]The profile of subjective effects has differed across replications with the same drug, largely due to differences in sample size. None of these differences have been qualitative but are largely differences in whether a trend reaches significance. In addition, Schuster and Johanson (1988) have reported a similar comparison across drugs, but it should be noted that their profile was obtained from drug discrimination studies. Even so, the general results are remarkably similar to those obtained in drug self-administration studies reported in this table.

[4]Analyses were only done using the Arousal scale (Johanson and Uhlenhuth 1978).

[5]A “yes” indicates that liking score for drug exceeded liking score for placebo, “no” indicates similar levels of liking or a placebo score greater than drug, and “NE” indicates that drug liking was not evaluated. See footnote[2] for further details.

the results will be discussed in later sections of this paper, but because this study also did extensive analyses that examined the relationship between preference and subjective effects, this study is also important in demonstrating the close correspondence between these two measures.

The participants (N=31) for the analysis were selected from a larger group of 52 on the basis of their drug choices in an experiment that tested preference between 5 mg *dl*-amphetamine and placebo (de Wit et al., 1985; 1986b). In general, the procedure used in this study was similar to the original study except that the ARCI which is described by Jasinski and Henningfield (this volume) was also used to evaluate subjective effects. As in the original study, there was a significant preference (63 percent) for amphetamine which is impressive given its dose (racemic amphetamine is less potent than *d*-amphetamine). Relative to the previous study (i.e., Johansonand Uhlenhuth 1980a) a greater numberof participants chose placebo on all five choice opportunities, perhaps due to the use of the racemic mixture. Therefore, it was possible to form two contrasting groups for comparison by selecting participants from the extremes of the distribution. The 20 participants who chose amphetamine on each of five sessions were designated choosers, whereas the 11 who chose placebo on all five sessions were designated non-choosers. The subjective responses to *dl*-amphetamine differed markedly between the two groups, the drug having in some cases opposite effects on mood. Relative to placebo scores, amphetamine increased Depression and Anxiety scores in the non-choosers whereas it decreased Depression scores and had no effect on Anxiety scores in the chooser group (figure 3). In contrast, the drug increased scores on Friendliness, Elation, Positive Mood, MBG, BG (not shown) and A (not shown) scales in the choosers, while it had no effect or decreased scores on these scales in the non-choosers (figure 4). Therefore, it appears that there is a logical relationship between choice and subjective effects. Amphetamine produced positive effects in the choosers with no aversive-like effects whereas in non-choosers, the only significant changes in mood are best described as negative.

In summary, psychomotor stimulants differ both in terms of preference and subjective effects and as just demonstrated, there is a striking correspondence between these two measures, at least under the conditions reported. As a whole, the results correspond well with those obtained using animal drug self-administration techniques and similar predictions would be made from both types of approaches in terms of dependence potential. While these similarities indicate the usefulness of the choice procedure in humans for assessing dependence potential, validity estimations are limited by the difficulty of comparing these results to sound epidemiological evidence. This problem is discussed by Senay (this volume) and Anthony and Trinkoff (this volume).

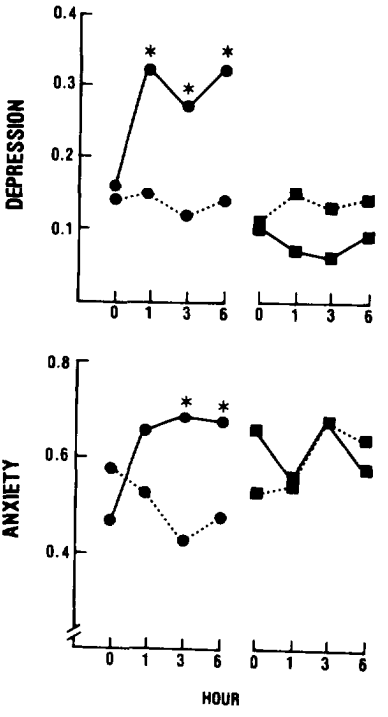

Figure 3: *Subjective effects of 5 mg dl-amphetamine in non-choosers (AN; left panels) and choosers (AC; right panels) on two scales (Depression and Anxiety) of the POMS. The dashed lines refer to mean scores on placebo sampling sessions, solid lines refer to mean scores on amphetamine sampling sessions. Asterisks refer to points at which drug and placebo scores differed significantly.*

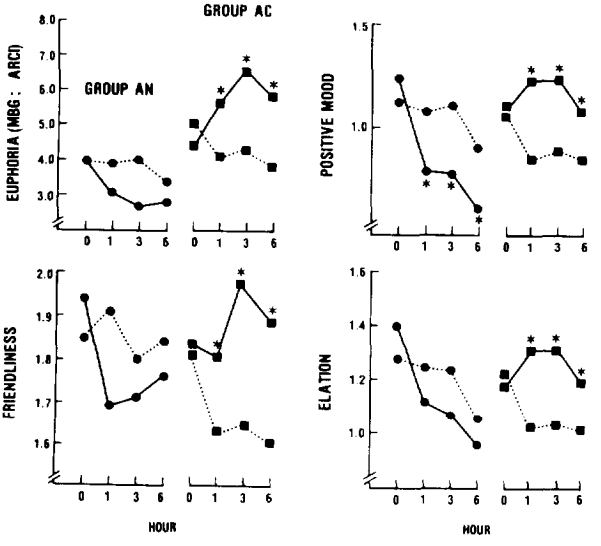

Figure 4: *Subjective effects of 5 mg dl-amphetamine in non-choosers (AN; left panels) and choosers (AC; right panels) on the MBG scale of the ARCI and three scales (Positive Mood. Friendliness, and Elation) of the POMS. The dashed lines refer to mean scores on placebo sampling sessions, solid lines refer to mean scores on amphetamine sampling sessions. Asterisks refer to points at which drug and placebo scores differed significantly.*

DISCRIMINATIVE STIMULUS PROPERTIES OF PSYCHOMOTOR STIMULANTS

Although the present review focuses on the use of choice procedures for assessing the reinforcing properties of drugs in humans, Bigelow and Preston (this volume) have made a clear case for the relevance of drug discrimination methods in assessments of dependence potential. Our group at the University of Chicago has also conducted a series of drug discrimination studies using the same psychomotor stimulants evaluated in the choice procedure and the results obtained in these studies contribute to the overall assessment of the dependence potential of this group of compounds (Chait and Johanson 1989; Chait et al., 1984, 1985, 1986a, 1986b).

The procedure used to assess the discriminative stimulus (DS) properties of psychomotor stimulants in humans was designed to parallel typical animal drug discrimination studies, with the substitution of a verbal response for the usual lever-press or key-peck response. In addition, the subjective effects of the drugs were concurrently measured, as described for the choice studies, to be able to also evaluate the correspondence between these two measures (see Schuster and Johanson 1988 for a discussion of this issue).

The participants were recruited in the same manner and with the same characteristics as participants in the self-administration studies. In all of the studies (although there were minor variations in protocol), participants were told that their job was to learn to discriminate between two different capsules, "Drug A" and "Drug B," based on the effects produced by each. One of these capsules contained 10 mg d-amphetamine and the other contained placebo. Participants reported to the laboratory in the morning three days per week throughout a 7- to 9-week study. Upon arrival, they filled out subjective effects questionnaires and then ingested a capsule. As in the choice studies, they were then free to leave for the day, taking additional questionnaires with them to fill out 1, 3, and 6 hr later. In the first four sessions of the study (sampling phase) participants were allowed to sample Drug A and Drug B, which were identified as such prior to ingestion. The next seven sessions (training/assessment phase) participants were given either Drug A or Drug B, i.e., amphetamine or placebo, in random order, but were not told at the time of ingestion which drug they were receiving. Six hours later they were instructed to telephone the experimenter and report which drug (A or B) they believed that they had received. If a participant's report was correct, he/she received a monetary bonus the next time they came to the laboratory. In order to progress to

the third, test phase, participants were required to correctly identify amphetamine and placebo on six of the seven training days, or on five consecutive training days.

In the four studies that have been conducted, 53 of the 100 participants learned the discrimination as defined by the criteria above. Post-hoc analyses revealed that all participants experienced subjective effects typical of those for stimulant drugs although there was a tendency for the discriminators to be more sensitive (Chait et al., 1989b). The 53 participants that learned the discrimination entered the test phase. The test phase consisted of test days interspersed with approximately the same number of additional training days. Test days were exactly the same as training days except that participants were not informed when they telephoned whether or not their drug identification was correct. On test days both responses were equally reinforced with money and participants received no feedback as to which drug they had received. Participants did not know when test days were scheduled and did not find out it was a test day until after they had telephoned and reported their identification. During each of the four studies, different drugs were evaluated during the test phase as follows:

Study 1 (N=17):	Placebo, 10 mg diazepam, 2, 5, and 10 mg d-amphetamine.
Study 2 (N=27):	Placebo, 10 mg d-amphetamine, 25 and 50 mg phenmetrazine, and 20 and 40 mg fenfluramine.
Study 3 (N=20):	Placebo, 10 mg d-amphetamine, 25 and 75 mg PPA and 0.5 and 2 mg mazindol
Study 4 (N=36):	Placebo, 10 mg d-amphetamine, 100 and 300 mg caffeine, and 25 and 50 mg benzphetamine.

In Study 1, seven participants learned the discrimination between placebo and 10 mg *d*-amphetamine. When tested with these training drugs, they responded correctly. Participants identified 2 mg amphetamine as placebo and at the 5 mg dose, the capsule was identified as placebo 50 percent of the time across participants. Diazepam was identified as placebo by five of the seven participants and produced a profile of subjective effects typical for a benzodiazepine. In Study 2, 14 participants learned the discrimination and identifiedphenmetrazine at both doses as amphetamine. The low dose of fenfluramine was identified as placebo whereas the high dose produced intermediate levels of amphetamine-appropriate

responding, reflecting both within- and between-subject variability. In Study 3, 12 participants learned the discrimination and identified the high doses of both mazindol and PPA as drug. The lower doses were identified as placeboor the identifications werevariable. In Study 4, 20 participants learned the discrimination and did not reliably identify either caffeine or benzphetamine as amphetamine. Figure 5 summarizes these results for the higher dose of each drug tested.

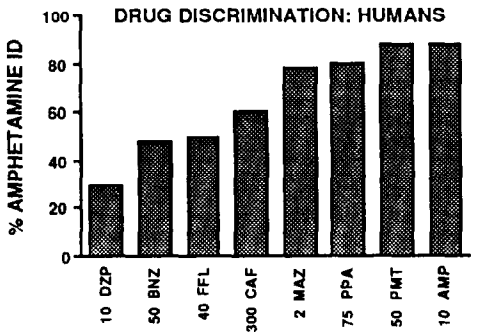

Figure 5: *The percent of participants who identified different psychomotor stimulant drugs (BNZ=benzphetamine; FFL=fenfluramine; CAF=caffeine; MAZ= mazindol; PPA=phenylpropanolamine; PMT= phenmetrazine; AMP= amphetamine) and diazepam (DZP) as amphetamine-like in the drug discrimination experiments described in the text. The dose of the drug in mgs* is *also indicated. This dose was the highest dose tested.*

The profile of subjective effects of drugs (i.e., fenfluramine anddiazepam) that did not substitute for amphetamine differed from amphetamine. On the other hand, phenmetrazine and the high dose of PPA which substituted for amphetamine produced subjective effects that were similar to amphetamine. However mazindol, despite the fact that the high dose substituted for amphetamine, as a DS produced subjective effects that differed somewhat from those of amphetamine. More specifically, mazindol's subjective effects were restricted to increases in anxiety, an effect also produced by amphetamine (Schuster and Johanson 1988). Since these anxiety-increasing effects (as well as the more positive effects such as increased Arousal) were also seen withphenmetrazine, it is possible that they were the basis of the discrimination.

In summary, the results of the four studies described above indicate that it is possible to train humans to discriminate 10 mg d-amphetamine from placebo using a procedure that 1) does not require laboratory space, 2)

limits exposure to drugs by using low doses and a relatively short experimental protocol, and 3) in many ways is comparable to procedures utilized in animal studies. On the other hand, only half of the participants learned the discrimination which may indicate that additional methodological studies would be desirable to improve training. Nevertheless, in those participants who learned the discrimination, the results were similar to those seen in animals. That is, phenmetrazine, mazindol and PPA, but not fenfluramine or benzphetamine, have been shown to substitute for amphetamine as a DS in rhesus monkeys (de la Garza and Johanson 1987). Furthermore, there is some indication that the discrimination is responsive to dose and is also pharmacologically specific since diazepam was identified as placebo. Finally, the subjective effects produced by the drugs that shared DS properties with amphetamine were similar but not identical.

Interestingly and relevant to the present context of utilizing drug discrimination procedures in the assessment of dependence potential, the results obtained in the self-administration studies and the drug discrimination studies had some striking differences. Amphetamine and phenmetrazine both were reinforcers and were similar as DS. On the other hand, mazindol and PPA were not self-administered by humans yet were discriminated as amphetamine. Their subjectiveeffects (see Schuster and Johanson 1988 as well as table 2) were similar but certainly not identical. Finally, benzphetamine was preferred in the choice procedure but was not identified as amphetamine-like despite similar subjective effects. These contrasts are intriguing and indicate the need for additional studies in this area.

REINFORCING PROPERTIES OF OTHER BENZODIAZEPINES

The failure to find that diazepam was preferred over placebo was surprising because this drug had been shown in previous human studies using sedative abusers to maintain self-administration behavior (see Roache and Griffiths, this volume). However, animal studies have clearly demonstrated that benzodiazepines are not robust reinforcers (Ator and Griffiths 1987). These findings stimulated a series of studies todetermine whether various pharmacological or environmental variables could modify the reinforcing properties of diazepam. One group of studies was designed to assess the reinforcing properties of benzodiazepines with different profiles of action

(de Wit et al., 1984a,b)[6]. This is an example of altering a pharmacological variable but can also be viewed as a systematic replication of the original finding.

Using the same procedure, two additional benzodiazepines, flurazepam and lorazepam, were tested. Flurazepam was selected because studies in rhesus monkeys indicated that this drug had more robust reinforcing properties, at least when tested in monkeys trained to self-administer pentobarbital (Johanson 1987). Relative to diazepam, lorazepam has a plasma half-life appreciably shorter (Greenblatt et al., 1976) which may augment its reinforcing properties (Griffiths et al, 1981). Despite these differences, neither flurazepam (15 and 30 mg) nor lorazepam (0.5, 1, and 2 mg) was preferred over placebo and in fact, as dose increased, placebo choice increased. Like diazepam, the higher dose of flurazepam increased Fatigue and decreased Vigor and Arousal scores on the POMS (de Wit et al., 1984a). These effects peaked slightly later than those of diazepam. Similar subjective effects were found for lorazepam but it was striking that these effects increased over the 6-hr measurement period which does not support the idea of a shorter duration of action (de Wit et., 1984b). Taken as a whole, the studies with diazepam, flurazepam, and lorazepam indicate that under the conditions of these experiments, benzodiazepines have minimal reinforcing properties in normal human volunteers.

INDIVIDUAL DIFFERENCES IN REINFORCING PROPERTIES OF DIAZEPAM

Although the extent of abuse of the benzodiazepines is not known with certainty, there are numerous case histories of individuals who use diazepamrecreationally. Furthermore, diazepam ranks high in emergency room mentions reported by the DAWN system, which presumably indicates that it is abused. Our failure to demonstrate reinforcing properties in normal volunteers and the contrasting findings in sedative abusers (Roache and Griffiths, this volume) indicated the need for additional studies that would attempt to isolate variables that increase the reinforcing properties of this class of drugs. One type of variable may be the behavioral and/or pharmacological history of an individual. For instance, Barrett (1987) has shown that the response of animals to pentobarbital canchange dramatically following a history of morphine administration. Since history

[6] Additional studies have also been done with other sedative drugs such as alcohol. However, because the use of these drugs necessitated a change in procedure, the results will be reported in a subsequent section describing a series of studies conducted within the confines of the laboratory.

is difficult to manipulate with human participants, we posed the question in terms of whether there are preexisting individual differences (e.g., personality traits, history of barbiturate abuse) that place certain individuals "at-risk" for finding benzodiazepines reinforcing. In identifying at-risk factors, it should be noted that strong preference for a drug in an experimental context is not an indicator that a specific research participant (or someone with similar characteristics) will abuse that drug because many environmental factors can inhibit such drug use. But relating individual differences to different reinforcing effects of drugs under laboratory conditions may shed light on factors involved in a high risk for drug abuse. The study of the relationship between individual differences and reinforcing properties demonstrates one of the advantages of using non-drug abusing populations of participants. In addict populations who have already indicated by their previous drug abuse history that a drug is a reinforcer, it would be unlikely that individual differences in reinforcing properties would emerge in an experimental context.

In addition to using *post-hoc* analyses for determining whether certain characteristics are correlated with differences in reinforcing properties, epidemiological studies may also provide clues concerning types of individuals who appear at risk for abusing benzodiazepines. Thus, the strategy in our studies was to determine whether the reinforcing properties of diazepam were different in participants selected on the basis of certain traits. In some sense studies using addict populations employ a similar strategy, i.e., participants are preselected for their preference for the test drugs. But determining that previous abuse of diazepam predicts that it has reinforcing properties is circular, although such studies may be extremely beneficial in determining whether new anxiolytics will substitute for diazepam and thus have a similar dependence potential at least in those already abusing sedatives.

Finally, it is important to use non-drug abusing populations for assessing the relationship between subjective response to drugs and their reinforcing properties. The subjective responses of previous heavy drug users are undoubtedly altered by this previous history so their possible causal relationship to drug-using behavior is hard to assess. Participants without this history can show a range of response to the test drug and these individual differences in subjective response may predict differences in reinforcing properties and provide clues to risk factors.

Choosers vs Non-Choosers

In a previous section, individual differences between choosers and non-choosers of amphetamine were described using a pool of 52 participants (de Wit et al., 1986a). These same participants were also tested in a preference experiment comparing 10 mg diazepam to placebo and, as in the amphetamine experiment, variability wasobserved among participants in terms of diazepam choice. The 27 participants who chose placebo on all five sessions were designated non-choosers. Because the number of 5-time choosers was small (N=7), thediazepam-choosing group included both 4- and 5-time choosers (N= 10). These two groups differed in their response to diazepam. Diazepam decreased Arousal and increased Fatigue in the non-choosers but produced no changes in these scales in the choosers. Furthermore, in the absence of diazepam (i.e., placebo sessions), non-choosers scored higher on Vigor, Friendliness and Elation on the POMS. When diazepam was administered, these differences disappeared, i.e., the drug decreased Vigor, Friendliness and Elation in the non-choosers and had no effect in the choosers. The relative insensitivity of the chooser group to the effects of diazepam was also reflected in their inability to correctly identify the drug as a tranquilizer. It appears that the choosers were simply unable to discriminate diazepam and their consistent choice of the capsule containing 10 mg diazepam, in the absence of discriminable differences, had no pharmacological basis. In the context of searching for characteristics that place individuals at risk, the low scores of choosers on the Vigor, Friendliness and Elation scales in the absence of drug were intriguing but not particularly helpful for purposes of prediction. Furthermore, when demographic characteristics and personality test scores were compared, there were no differences between choosers and non-choosers.

Populations with Pre-Existing Anxiety

The idea that excessive drug use is an attempt to self-medicate is not new, but has received relatively little experimental support (see Schuster&., 1979). In fact, experimental studies in both humans and animals have supported the view that most drugs of abuse produce direct positive reinforcing effects that are unrelated to psychopathology. While self-medication may not play a role in the misuse of drugs such as stimulants with unequivocal positive reinforcing properties, the misuse of drugs like diazepam that appear to have minimal reinforcing properties may depend on other factors such as therapeutic efficacy. It is conceivable, therefore, that diazepam might have reinforcing properties in participants with increased levels of anxiety. Furthermore, if this is the case, these individuals are at special risk because they are more likely to be prescribed diazepam.

To test the relationship between anxiety reduction and reinforcing properties, four groups of volunteers were recruited differing in levels of anxiety (de Wit et al., 1986b; McCracken et al., in press). Anxiety was assessed using the Taylor Manifest Anxiety Scale (TMAS), the Spielberger Trait Anxiety Inventory (STAI), the Hopkins Symptom Checklist (HSCL), and a psychiatric interview. The control group (CTRL) consisted of healthy adults with TMAS, STAI, and HSCL anxiety scores within a normal range. A second group (ANX) had high scores on the TMAS and STAI but did not meet DSM-III criteria for any anxiety disorder. The third group (ANX-DSM) did meet DSM-III criteria for Generalized Anxiety Disorder. A fourth group (ANX-Rx) was recruited at a later time after it was determined that this third group, despite their diagnosable anxiety did not wish to receive treatment. The ANX-Rx group was identical to the ANX-DSM group except that they answered a recruitment advertisement that asked for participants who were anxious and wished to receive treatment for their disorder. Except for level of anxiety, the four groups did not differ on any other measurable dimension.

Table 3 summarizes the sex, age, and anxiety questionnaire scores for the four groups. The HSCL anxiety score was highest in the ANX-Rx and ANX-DSM groups, intermediate in the ANX group, and lowest in the CTRL group. The STAI and TMAS scores, which were used as selection criteria for the ANX but not the other anxiety groups, differentiated all of these groups from the CTRL group and tended to increase across groups (see table 3). In addition, on the Anxiety scale of the POMS, all anxious groups had higher scores under non-drug conditions. The concordance of these measures, particularly those that were not used as criteria for recruitment, indicate the reliability of the anxiety classification of the participants.

Table 3: Demographic and anxiety ratings[7]

	CTRL	ANX	ANX-DSM	ANX-Rx[8]
N	12	11	13	14
Mean Age	26	27	27	32
Sex (M/F)	6/6	4/7	4/9	6/8
Mean STAI	29.9	44.7	49.1	53.9
Mean TMAS	9.2	22.8	27.1	
Mean HSCL	0.15	0.58	0.95	1.02

[7] Results are shown for 4 groups: CTRL=control group; ANX=group with higher ratings on the STAI and HSCL but who did not meet criteria for DSM-III Generalized Anxiety Disorder; ANX-DSM=group who did meet criteria for DSM-III Generalized Anxiety Disorder; and ANX-Rx=group that also met criteria for DSM-III Generalized Anxiety Disorder but who also answered advertisement that indicated that they wished treatment.

[8] TMAS was not administered.

As shown in figure 6, none of the groups of anxious individuals preferred diazepam to any significantly greater extent than found in Johanson and Uhlenhuth (1980b). Despite predrug differences in anxiety scores between the CTRL and the anxious groups, anxiety scores of all groups decreased following the administration of 10 mg diazepam. Thus, diazepam did exert a measurable anxiolytic effect, but this did not affect preference for the drug. Changes in the other subjective effects also showed no differences related to group and were similar to those reported in the previous experiment (Johanson and Uhlenhuth 1980b). Clearly, these results do not support the hypothesis that highly anxious individuals are at-risk for abusing benzodiazepines because of an increase in reinforcing properties as a function of reduced anxiety. This is not to say, however, that these individuals are not at-risk becauseof theirincreasedprobability of chronic exposure to anxiolytics. That is, afterrepeated administration, itispossible that reinforcing properties will emerge, perhaps due to the development of tolerance to sedative properties, the development of physical dependence, or increased sensitivity to effects that are not observed following acute administration. Recruiting participants with a long history of treatment with benzodiazepines might help to determine whether long-term changes occur.

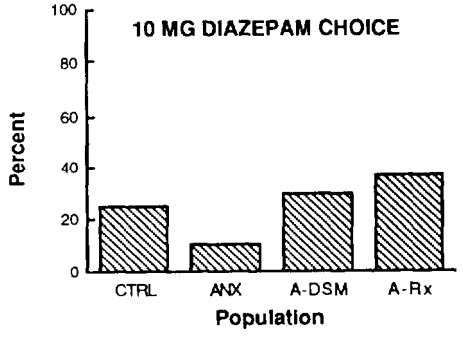

Figure 6: *Choice results for different populations of participants differing in preexisting levels of anxiety in a comparison between 10 mg diazepam and placebo. The ordinate is the percentage of participants who chose diazepam and the abscissa indicates the different populations (CTRL=control group; ANX=group with higher ratings on the STAI and HSCL but who did not meet criteria for DSM-III Generalized Anxiety Disorder; ANX-DSM=group who did meet criteria for DSM-III Generalized Anxiety Disorder; and ANX-Rx=group that also met criteria for DSM-III Generalized Anxiety Disorder but who also answered advertisement that indicated that they wished treatment.)*

Older Populations

One population of individuals that has a greater incidence of long-term benzodiazepine use is older people (Mellinger et al., 1984). This may indicate that the reinforcing properties of benzodiazepines are greater in these individuals, placing them at-risk for abusing benzodiazepines. In order to determine whether older people are more likely to find diazepam reinforcing, we designed a study using participants who were older than those that had previously been used in our experiments (de Wit et al., 1985). Participants were recruited who were between 40 and 55. It would have been desirable to recruit even older participants but the increased probability of medical complications prohibited this strategy. Except for the age of the participants, the experimental protocol was identical to that previously described in all other respects. Individuals participated in three separate 9-week experiments comparing 5 mg *dl*-amphetamine and both 5 and 10 mg diazepam to placebo.

Age did not significantly alter the proportion of participants who chose either amphetamine or diazepam (5 and 10 mg). As in earlier studies, amphetamine was chosen overall more often than placebo, 5 mg diazepam as often as placebo, and 10 mg diazepam significantly less often than placebo. The participants' relative drug liking scores were consistent with their choice behavior. That is, most participants both chose and liked amphetamine more than placebo, whereas most participants preferred placebo to diazepam on both liking ratings and the choice measure. Drug identification was also similar across the two groups. Amphetamine was labelled as either "stimulant" or "placebo" by most participants, whereas diazepam was most often correctly labelled as "tranquilizer." Finally, although there was some evidence that older people were more sensitive to the subjective effects of amphetamine, their response to diazepam did not differ from the control group. At the 10 mg dose of diazepam, Vigor, Friendliness, Elation, Arousal, Positive Mood, BG, MBG and A scores were significantly decreased, whereas Fatigue, Confusion, PCAG and LSD scores were increased. The effects of both 5 and 10 mg were greatest 1 hr after drug ingestion, replicating the previous study.

Concluding Remarks

In summary, the studies designed to determine whether there are populations that might be at-risk for abusing benzodiazepines found no evidence that the reinforcing properties of diazepam were greater for these individuals. Thus, even thoughdiazepam effectively lowered anxiety

levels in several groups of anxious volunteers, these participants still preferred placebo to drug. There was some evidence that a subset of the group of anxious individuals who were seeking treatment reacted differently to diazepam but the number of individuals in this subset was too small for meaningful comparisons (see McCracken et al., in press). In addition, older people also did not prefer diazepam to placebo and like younger participants, preferred placebo over 10 mg diazepam. Finally, a closer examination of those individuals who chose 10 mg diazepam four to five times only showed that as a group, these participants tended to be less sensitive to the mood-altering properties of diazepam. Thus, while it is likely that there are individual characteristics that place some individuals at-risk for abusing diazepam, the only experimental evidence as of 1986 was that individuals with a previous history of sedative abuse self-administered diazepam above placebo levels (Griffiths et al., 1979). It was our hope that additional research would reveal other types of predictors more useful than an already established history of abuse.

THE EFFECTS OF ENVIRONMENTAL CONTEXT ON THE REINFORCING PROPERTIES OF SEDATIVES

In our previous studies, participants reported to the laboratory in the morning to take their capsule and were then free to conduct their normal activities outside the laboratory. Although these conditions have the advantage of being relatively naturalistic, other environmental demands on the participants during the day may rule against their selection of sedative drugs. That is, even at the relatively low doses of diazepam used in these previous studies, their sedative properties may have interfered with the participants' ability to work or study during the day, and this negative effect may have overridden the positive properties of the drug. In addition, the strategy of allowing participants to leave the laboratory makes it difficult to evaluate the reinforcing properties of prototypic sedative drugs of abuse such as alcohol (imagine having your subjects show up for work with alcohol on their breath) and limits the doses of sedatives that can be administered. In studies by Griffiths and his colleagues (Griffiths et al., 1979) that have shown that diazepam is a positive reinforcer, doses up to 200 mg have been used. Although the participants in those studies were undoubtedly tolerant to the sedative effects of benzodiazepines because of previous experience with that class of drugs, it is possible that reinforcing properties only occur at higher doses. All of these considerations led to additional studies designed to minimize the impact of diazepam's sedative properties on drug choice.

The Effects of Time of Day on the Reinforcing Properties of Diazepam

In order to minimize the possible disruptive effects of diazepam on the evaluation of its reinforcing properties, alterations were made in the environmental context of its administration. In the first study (de Wit et al., 1985), the experimental protocol was identical to the previous experiments except that participants reported to the laboratory in the late afternoon so that peak drug effects occurred in the early evening, a time more consistent with recreational drug use ("cocktail hour"), i.e., when other demands on the participants' attention are presumably less. Participants in this study were tested in three separate experiments evaluating preference for 5 mg &amphetamine, 5 mg diazepam, and 10 mg diazepam, and their results were compared to a control group tested concurrently which received drug at the usual morning time. Despite this change, however, preference for diazepam remained low, i.e., as in previous experiments, placebo was clearly preferred over 10 mg diazepam, and 5 mg diazepam and placebo were equally chosen. As a whole, the subjective effects produced by diazepam were similar in both the experimental and control group. However, there were some differences in subjective effects in the group tested in the late afternoon. For instance, not surprisingly, Fatigue scores on the POMS were higher for the afternoon group regardless of the drug administered. The subjective effects produced by 5 mg &amphetamine were less pronounced and there was also a tendency for both a slightly lower preference for amphetamine in both the choice test and the liking ratings, suggesting that the later time of drug administration attenuated the reinforcing properties of amphetamine. Some participants even reported that this low dose interfered with their normal sleeping patterns, an effect that may have contributed to their decreased preference and liking. Nevertheless, experiencing the effects of diazepam at this later time did not influence its reinforcing properties.

The Effects of Remaining within the Laboratory on the Reinforcing Properties of Diazepam

The persistent avoidance of diazepam across experimental conditions that involved participants not remaining within the laboratory environment may be attributable to the population that was recruited for these investigations. Most of the participants in the previous studies were students and others had busy schedules. Such people may find sedative effects aversive regardless of the time of day. Even though individuals who were employed evenings or nights were not accepted into the late afternoon study, the participants may have planned evening activities

requiring concentration, such as studying. The participants in these studies also did not report recreational sedative use and most particularly were relatively light alcohol drinkers (see table 4). Thus, they may generally avoid sedative drugs because of work/study demands. To circumvent this problem, two additional strategies were used to assess the reinforcing properties of diazepam: 1) recruit non-drug abusing populations who have demonstrated that they do not avoid sedative drugs in their normal day-to-day routine, and 2) arrange the environmental conditions so that this property of sedative drugs has no significant functional consequence. The former strategy will be discussed in a later section. The latter strategy involved having participants remain within a laboratory environment, paying them for their time, but not allowing them to engage in task-related activities. Allowing participants to remain within the laboratory also allowed the administration of higher doses of diazepam.

In the first study (reported in de Wit et al., 1989a), experimental sessions were conducted over a 4-hr period in the evening and participants remained in the laboratory. The testing environment consisted of comfortably furnished rooms with a couch and upholstered chairs, and a television, movies, radio, audio tapes, and games were available. Participants could engage in leisure activities of their choice but they were not allowed to work or study. There were five experimental sessions, conducted at one week intervals, and participants were tested in pans. Thefirstfour sessions were sampling sessions with 20 mg diazepam alternating with placebo. During the fifth session, participants were given a single choice between the two distinctively colored capsules. Except for remaining in the testing

Table 4. Average alcohol consumption across studies

Group	N	Choice[9]	#Drinks per Week (SD)	Reference
Control	12	25	5.6 (4.3)	de Wit et al., 1986b
ANX	11	5	7.1 (6.7)	de Wit et al., 1986b
ANX-DSM	13	30	4.1 (2.9)	de Wit et al., 1986b
ANX-Rx	13	37	4.7 (5.6)	McCracken et al., in press
Older	11	38	3.0 (2.7)	de Wit et al., 1985
Afternoon	13	32	4.9 (4.2)	de Wit et al., 1985
Choosers	10	94	3.9 (3.3)	de Wit et al., 1986a
Non-Choosers	27	0	4.7 (5.6)	de Wit et al. 1986a
Laboratory	11	27	6.4 (8.5)	Unpublished[10]

[9] Percent choice for 10 mg diazepam over placebo.
[10] Portions of this study are reported in de Wit et al., 1989a

rooms, the protocol was similar to the previous studies in other respects. For instance, participants reported to the laboratory, filled out subjective effects questionnaires, and ingested a capsule. During the course of the evening, additional questionnaires were filled out at regular intervals.

Despite these changes in the experimental conditions, preference for diazepamremained low. Eight of the 11 participants (73 percent) preferred the placebo capsule to the capsule containing 20 mg diazepam and the subjective effects produced by diazepam were typical of sedative-like drugs.

The Effects of Remaining within the Laboratory on the Reinforcing Properties of Diazepam: Multiple Drug Administrations

One of the problems of conducting the experiments within the laboratory setting relative to the studies where participants were free to leave was that it required more time to complete studies with similar numbers of participants and the time demands per participant increased. In fact, one of the reasons for using only a single choice session in the previous diazepam choice study was to reduce the individual time demand factor. However, based upon an analyses of previous choice data obtained with five choice sessions, it was determined that initial choice did not reliably predict overall choice but that the first threechoice sessions did. Therefore, it was necessary to increase the number of sessions to seven (four sampling and three choice), lengthening the experiment even more. All of these changes made it difficult to test a wide range of doses, i.e., conduct multiple experiments with each participant. In order to increase the efficiency of the experimental protocol, the choice procedure was altered to allow participants to sample a wider range of doses (de Wit et al., 1988a). In most respects, the protocol was similar to the laboratory study just described except for two additional choice sessions. However, during sampling, the total dose of 20 mg diazepam was administered in five divided doses (4 mg each) separated by 30 min intervals. This cumulative dosing procedure allowed participants to experience the effects of low as well as higher doses of the drug. On choice sessions, participants first indicated which drug they wished to take on that session, and they were required to ingest one dose at that time. For the remainder of the session, they were given options every 30 mins to take up to six additional doses of the same drug (a total of 28 mg). Thus there were two measures of preference: 1) the number of sessions on which participants chose diazepam over placebo, and 2) the number of doses of diazepam they ingested within a session. A further change in procedure was that the four participants in each group were acquainted prior to the study and the drug administered during sampling was the same for all of them.

This change in procedure had a remarkable effect upon diazepam choice. Overall, diazepam was chosen on 67 percent of the sessions. Eleven (61 percent) of the 18 participants chose diazepamon all three choice sessions while five (28 percent) exclusively chose placebo (see figure 7). On sessions when they chose diazepam, participants ingested an average dose of 15.6 mg (3.9 capsules). When they chose placebo, participants took on average only 1.6 capsules. Individuals who took diazepam on all three sessions also took more doses (16.4 mg) of the drug within sessions than the 1(4 mg) or 2 (10 mg) time chooser. Further analyses were done after dividing the participants into two groups based upon the amount of drug (i.e., mg's) they ingested during choice sessions (see figure 7). The low dose choice group chose diazepam over placebo on one out of three sessions, taking an average dose per choice session of 4.9 mg, or 1.2 capsules, whereas the high dose choice group chose diazepam on all three choice sessions and ingested an average dose of 18.8 mg per session, or 4.7 capsules. The low dose choice group also chose about as many "doses" of placebo as diazepam. Using a measure of psychomotor performance, we showed that diazepam decreased performance but there were no differences between the two groups in this effect. Despite the increased choice of diazepam as well as the emergence of a group of participants who consistently chose diazepam, the subjective effects of 20 mg diazeparn given in divided doses were typical for sedatives, i.e., decreases in Vigor, Arousal, Positive Mood and Elation, and increases in Fatigue and Confusion of the POMS, and these effects were the same for both the low and high dose choice groups. There were no indications of any subjective effects even in the group of consistent choosers that could be considered positive (this finding should be compared to the results with alcohol reported below). This is a striking example of a divergence between preference and measures of subjective effects and is a warning that both of these measures are necessary for a complete assessment of a drug's effects.

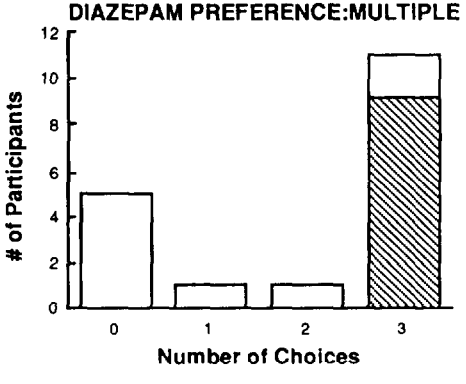

Figure 7: *The number of participants who chose diazepam on 0 to 3 of the choice sessions in the multiple dose experiment. The shaded area indicates the participants in the high dose choice group. The remaining participants (open bars) were in the low dose choice group.*

At the present time, it is not clear why diazepam choice increased dramatically. As just discussed, the increased preference does not seem to be related to altered subjective effects. A major difference between the present study and others was the use of the divided cumulative dose regimen. This allowed participants to experience a wider range of doses during the sampling sessions and regulate their dose during the choice sessions. It is interesting to note that even in the participants who chose diazepam on every session, their dose preference was below the 20 mg experienced during sampling. The use of the flexible choice paradigm may have allowed participants to select a dose (approximately 16 to 18 mg) that was maximally reinforcing. However, both 10 and 20 mg diazepam have been tested in previous experiments and it is difficult to believe that the failure to test doses of 16 to 18 mg contributed to the failure to demonstrate reinforcing properties in those previous studies. On the other hand, having control over time of dose administration may be an important factor, although additional studies are clearly needed to evaluate this possibility. In addition, the present study also differed in two other respects unrelated to the dosing regimen. First, the participants were tested in groups of four who were acquainted prior to the experiment. This strategy was used to increase participation as well as create a more social and relaxed atmosphere than would have existed if strangers were tested together, as in the previous laboratory study. In addition, all individuals within a group of four received drug or placebo on the same sampling session. It is known that drug use is influenced by social variables and it would be interesting to vary these social variables in future studies.

THE REINFORCING PROPERTIES OF ALCOHOL

In addition to diazepam, we have also tested the reinforcing properties of alcohol. These studies necessitated the use of a laboratory setting because of our unwillingness to have participants continue to engage in their normal activities under the detectable influence of alcohol. We were interested in evaluating the reinforcing properties of alcohol because this drug is a prototypic sedative drug of abuse but also because it is known that individuals differ in their subjective response to alcohol. This study, therefore, sought not only to determine the reinforcing properties of this drug in comparison to diazepam but also to determine the relationship between alcohol self-administration and mood effects in light to moderate social drinkers who did not have a history of heavy alcohol consumption. Individuals with a history of alcoholism or alcohol-related problems were not accepted because of the possibility of an altered response. Sessions

were conducted three evenings per week in the comfortable setting previously described and efforts were made to minimize any possible disruptive effects that might be produced by alcohol by only allowing the participants to engage in leisure activities. As in the diazepam experiment, groups of three to four individuals participated concurrently, with a total of 29 participants. However, these participants were not acquainted prior to the study. The dose of alcohol was 0.5 g/kg and half of the participants in each group received drug and half placebo during the four sampling sessions.

Overall, alcohol was only preferred on 50 percent of the choice sessions and there were marked individual differences in preference. That is, as shown in figure 8, one subset of participants never chose the alcohol-containing drink, others chose it once or twice, and another subset chose alcohol on all three sessions. These subsets also differed in their subjective response to alcohol as measured by the POMS. Comparing across the two extreme groups (consistent choosers and non-choosers) showed that alcohol increased Elation, Vigor, Arousal and Positive Mood scores, and decreased Fatigue in the choosers whereas in the non-choosers alcohol decreased Elation, Vigor and Arousal and increased Confusion scores. Interestingly, on a test of psychomotor performance, alcohol decreased performance similarly regardless of preference. In

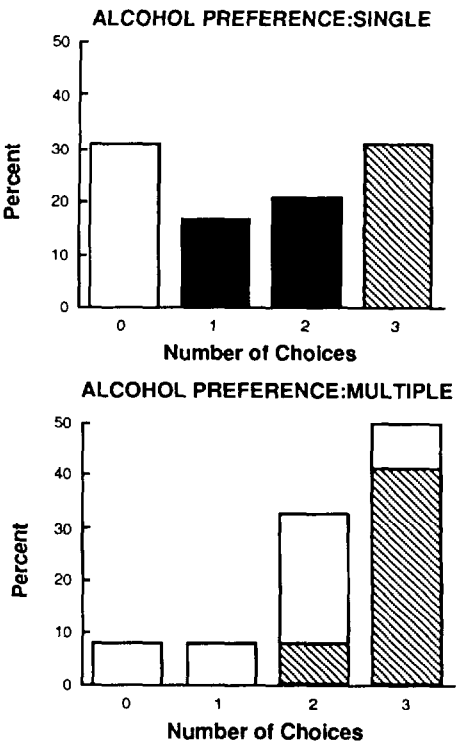

Figure 8: *The percentage of participants that chose alcohol on 0 to 3 of the choice sessions in both the single dose procedure (top panel) and the multiple dose procedure (bottom panel). The stippled area indicates consistent 3-time choosers in the single dose experiment and high dose choosers in the multiple dose experiment. The open bars indicate consistent placebo choosers in the single dose experiment and low dose choosers in the multiple dose experiment.. The solid bars indicate inconsistent choosers in the single dose experiment.*

general, those participants who always chose the alcohol-containing beverage were more likely toconsume drugs recreationally. For instance, those participants consumed an average of 14.1 alcohol drinks per week whereas the remaining participants consumed less than 8 per week.

The second study with alcohol (de Wit et al., 1989b) used the multiple dose procedure previously described for diazepam. As in the previous study, one of the purposes of this study was to examine individual differences, i.e., whether there was any preexisting characteristic or difference in response to the ingestion of alcohol that could be related to choice. We believed that the multiple dose procedure was especially relevant for studies with alcohol since this drug is known to have biphasic effects dependent on dose and is typically used recreationally in divided doses. Therefore, by using the cumulative dosing procedure, participants would be exposed to both low and high doses. It was expected that if sedative properties produced by doses that were too high for a particular individual had mitigated against choosing alcohol in the previous study, in the multiple dose procedure these types of individuals would choose alcohol, thereby increasing overall choice, but they would then select fewer additional doses of the alcohol to consume during the remainder of the choice session. Furthermore, the procedure permitted participants to consume the drug in a naturalistic manner.

The protocol was similar to the diazepammultiple dose experiment except that the interval between alcohol doses was decreased to 15 min. Five doses of 0.1 g/kg were available during two sampling sessions and placebo was available during the other two sampling sessions. As in the diazepam experiment, choice involved two separate behaviors. The first was an initial selection of alcohol or placebo and the second was the selection of additional doses of the same beverage throughout the remainder of the session. Participants were permitted to take up to 10 additional doses, or a total cumulative dose of 1.1 g/kg. All other aspects (e.g., activities available; testingfourfriendsinagroupintheevening within a comfortable laboratory setting; number, length, and spacing of the experimental sessions; administration of subjective effects questionnaires; etc.) of the protocol were the same as in the diazepam cumulative dose experiment.

Relative to the previous study with alcohol, drug choice increased as was predicted. Participants chose the alcohol-containing beverage on an average of 75 percent of the choice sessions (figure 8) and only two participants chose placebo more than alcohol. Overall. the number of doses of alcohol ingested during choice sessions after it was selected was 8.3 or 0.83 g/kg, a dose higher than that administered during the sampling

sessions. The participants were divided into two groups, low and high dose choosers (note that these groups are not comparable to the consistent choosers and non-choosers compared in the previous alcohol study). It had been predicted that choosers of alcohol, which in the present experiment includes the majority of participants (only two chose placebo more than alcohol), could be divided into a group that chose doses of alcohol equal to or above 0.5 g/kg and a group that chose alcohol but kept their dose low to avoid the aversive sedative effects. While there were certainly two distinct groups (the average number of doses per session taken by the high dose choice group was 9.1 and for the low dose choice group, it was 5.4), overall alcohol dose in the low dose group was still above the dose used in the previous study, 0.5 g/kg. In addition, the two groups did not differ in terms of normal alcohol consumption, with means of 8.6 drinks per week for the low dose choice group and 8.7 in the high dose choice group. Thus it might be argued that the participants in the multiple dose experiment were not differentially sensitive to the effects of alcohol as were the participants in the singledose experiment. However, the analyses of the subjective effects produced by the fixed (but administered in divided doses) dose of 0.5 g/kg during sampling still showed opposite effects. In the high dose choice group, this dose of alcohol increased scores on Elation, Vigor, Arousal and Positive Mood,

Table 5. Subjective effects of alcohol

	SINGLE DOSE		MULTIPLE DOSE	
POMSSCALE	Chooser	Non-Chooser[11]	High Dose	Low Dose[12]
Elation	+	—	+	
Vigor	+	—	+	—
Arousal	+	—	+	—
Positive Mood	+		+	—
Fatigue	—		—	+
Confusion		+	—	+

[11]These results are from the nine participants in the single-dose alcohol study who consistently chose 0.5 g/kg alcohol (choosers) and the nine participants who consistently chose placebo on all 3 choice sessions (non-choosers). Total number of participants in the experiment was 29.

[12] These results are from the six participants who selected the highest number of alcohol doses when alcohol was selected and the six participants who selected the lowest number out of a total of 12 participants. Five of the former group selected alcohol on all three choice sessions with one choosing alcohol on two of the sessions. The other six participants chose alcohol on 3 (N=1). 2 (N=3), 1 (N=1) or 0 (N=1) choice trials.

relative to placebo. In contrast, in the low dose choice group, the drug decreased scores on Vigor, Arousal and Positive Mood. Alcohol also decreased Fatigue and Confusion scores in the high dose choice group, but it increased scores on these scales in the low dose choice group. The subjective effects of the low dose choice group were strikingly similar to those found for consistent non-choosers in the previous study (table 5) despite the amazingly high (66 percent) degree of choice of the low dose choice group in the present study. It appears, therefore, that across individuals, there are robust differences in subjective response to alcohol. These differences are somewhat predictive of choice since participants who experienced stimulant-like effects from alcohol in both experiments were 3-time choosers. However, participants who experienced sedative effects from the fixed dose of 0.5 g/kg varied in their alcohol choice across the two experiments.

Although it appears that changes in subjective effects cannot account for the differences in overall choice between the two experiments, there were many other factors which may have contributed to the higher degree of preference for alcohol in the multiple dose experiment. For instance, it is possible that the participants' ability to regulate their dose during the choice phase increased alcohol's reinforcing properties. Furthermore, in addition to the self-control allowed by the procedure, the use of divided doses is also more similar to the way that alcohol is ingested in naturalistic settings. However, this would not seem to be a factor for the diazepam experiment. Finally, the social conditions (i.e., group of friends all receiving the same substance during sampling sessions) discussed in the multiple dose diazepam experiment may have influenced the results.

REINFORCING PROPERTIES OF DIAZEPAM IN PARTICIPANTS WITH A HIGHER LEVEL OF ALCOHOL CONSUMPTION OUTSIDE THE LABORATORY

As previously discussed, the sedative properties of diazepam may make it a less efficacious reinforcer in certain settings. A major aim of the laboratory studies was to create an environment that minimized the functional consequences of these sedative effects. A second strategy was to select participants whose previous drug use history may indicate that they are either tolerant to these effects or at least they do not uniformly avoid drugs with sedative effects (e.g., alcohol). This strategy involved selecting participants who consumed higher levels of alcohol on a regular basis. We noted that participants in previous experiments were light drinkers of alcohol (table 4). The results of the initial alcohol experiment

showed that alcohol was preferred to a greater extent in participants who consumed at least 14 drinks per week, although this differential effect was not noted in the follow-up study. Nevertheless, epidemiological studies have indicated that individuals with alcohol problems are more likely to use as well as abuse benzodiazepines (Busto et al., 1983; Woods et al., 1987) so preference for alcohol might easily be a risk factor. Thus, it was reasoned that the reinforcing properties of diazepam might be higher in participants with a higher level of alcohol consumption.

Twelve participants were selected who met at least two of the following criteria for alcohol consumption: 1) consumes at least seven drinks per week, 2) consumes at least three drinks on a single occasion at least once a week, and 3) consumes alcohol on at least four days of the week. Individuals with any history of drug- or alcohol-related problems were not accepted. In all respects the experimental protocol was identical to the multiple dose procedure described above for diazepam and alcohol. On average, these 12 participants consumed 11.8 drinks/week in comparison to participants in the original diazepam multiple dose experiment that consumed 4.8 drinks/week, which is similar to the level of alcohol consumption for all of the prior experiments (table 4).

In striking contrast to all previous studies with diazepam, all twelve participants chose diazepam on all three choice sessions (de Wit et al., 1989a). In addition, they chose an average dose of 25.2 mg per choice session, or 6.3 out of the 7 available doses which is much higher than the average for the 3-time choosers in the previous multiple dose diazepam experiment (16.2 mg). In some respects, the subjective effects of 20 mg diazepam during the sampling sessions in the present study were similar to those reported in the multiple dose experiment in light alcohol drinkers (figure 9). For instance, scores on Confusion and Fatigue increased whereas scores on Arousal decreased. However, there was also evidence that more moderate drinkers of alcohol experienced more positive effects following diazepam. Scores on Vigor, Elation (not shown), Positive Mood and Friendliness increased relative to placebo. Thus, there was a strange mixture of apparent positive and negative subjective effects. Participants reported increases in Fatigue, for instance, whereas they also reported increases in Vigor. To some extent, this mixture might be attributable to differences in time course (see figure 9). Nevertheless, increases in positive mood states such as Elation and Friendliness after diazepam have not previously been observed in individuals without a history of drug abuse. Even in the original multiple dose diazepam study, those participants who preferred diazepam on every occasion did not show such subjective effects. These findings suggest that even moderate

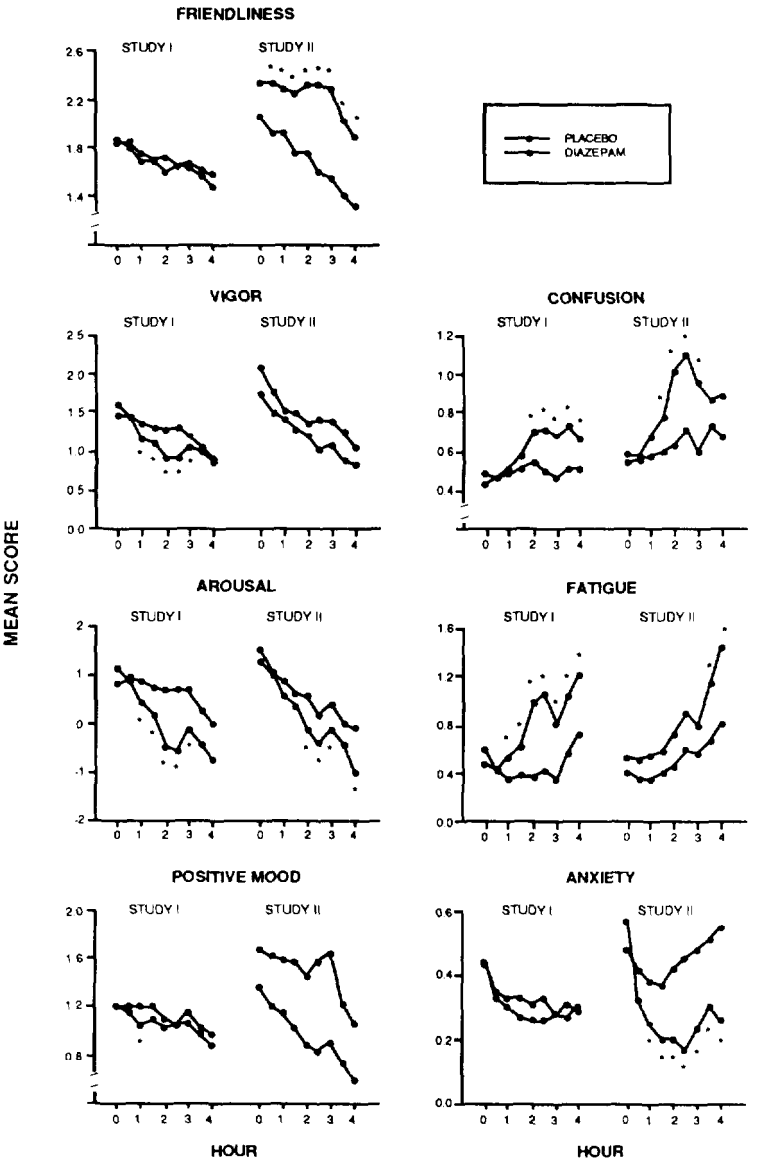

Figure 9: *Hourly mean POMS scores for diazepam and placebo sampling sessions far the experiment with light alcohol drinkers (Study 1: left portion of each panel) and far the experiment with moderate alcohol drinkers (Study II; right portion of each panel). Asterisks indicate significant differences between drug placebo means at each hour for scales on which significant drug-by-hour interactions were obtained.*

users of alcohol may be more likely to experience euphoric effects from diazepam. Moreover, both the relatively greater frequency of these individuals' choice of drug and the higher doses ingested on choice sessions indicate that the drug serves as an effective positive reinforcer. Thus both the positive subjective responses to the drug during the sampling phase and participants' drug-taking behavior during the choice phase were indicative of relatively greater liability for abuse.

Unfortunately, it is impossible to attribute the consistent choice of diazepam at relatively high doses to any single variable. The participants in this study were selected because they were heavy andregularconsumers of alcohol but they also differed on other preexisting variables compared to those volunteers that participated in previous studies. For instance, they were slightly older and fewer were students. In addition to drinking greater amounts of alcohol, their current and lifetime use of other drugs such as marijuana, tobacco, hallucinogens and opiates was greater, although by no means were these individuals drug abusers or did they have any drug-related problem. Finally, their attitude towards recreationally-used drugs was more positive. It is also difficult to assess the importance of the procedure. The use of the multiple dose protocol increased diazepam preference in a previous study with light drinkers. While it is possible that this variable was a major determinant of the results in the heavier alcohol consumers, this cannot be determined in the absence of another experimental group of heavier alcohol consumers tested under the single dose procedure. Furthermore, in both diazepam experiments using themultiple dose procedure the influence of the social variable of testing participants in a group of friends has not been determined. Despite the difficulty of unequivocally determining the major variable that increased the reinforcing properties of diazepam, these results do indicate that some individuals, under certain experimental conditions, find diazepam reinforcing and report mood effects that could be interpreted as positive. How the interaction between preexisting characteristics, such as moderate alcohol consumption, the experimental context of repeated drug administrations in a highly social environment, and the acute behavioral and subjective responses to diazepam occurs is not clear and will require additional studies to delineate the factors that may place some individuals at risk for abusing benzodiazepines.

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CHAPTER 10

Relationship Between Self-Reported Drug Effects and Their Reinforcing Effects: Studies with Stimulant Drugs

Marian W. Fischman, Ph.D.

INTRODUCTION

Traditional approaches to characterizing a drug's profile of action and assessing its abuse liability in humans have utilized a variety of self-report measures (e.g., Martin et al., 1971; Jasinski 1977). Researchers have predicted the abuse liability of the unknown compound based on the extent to which the profile of self-reports generated by an unknown drug is similar to that of a known drug of abuse (Fischman 1977). It has been assumed that "positive," "euphoria-like" effects are an indirect measure of a drug's reinforcing effects (Jasinski et al., 1974). Standardized questionnaires have been employed in determining the pattern of responses associated with the behavioral and physiological effects of pharmacologic agents and the profiles of drug effects thus obtained have provided a major basis for the prediction of the abuse liability of a broad range of compounds.

It has been argued (Schuster et al., 1981) that humans, asked to give a verbal response about the effect of a drug, are really utilizing the discriminative stimulus properties of the drug in the same way as animals required to differentiate between two drugs by depressing different levers. In both cases, the self-reporting response is an operant, maintained by its consequences. The monkey or rat is given careful lever press training to differentially respond todifferent drug stimuli, while humans have learned to apply labels (e.g., sleepy, happy, friendly, etc.) through differential reinforcement of these verbal responses as they grow up. In addition, non-human research subjects can also be shaped to respond to labels when given an appropriate conditioning history (Lubinski and Thompson 1988). Most humans have a relatively common conditioning history in

this regard, and the generality of such histories can be attested to by the generally similar verbal reports obtained within drug classes over a wide range of human subjects. The generality of these drug classes appears to extend across species since laboratory animals trained to respond differentially to different classes of drugs do so in a manner concordant with the differential profiles of self-reports generated by these same classes of drugs when administered to experienced drug users (see Schuster et al., 1981). The care with which these self-reported subjective effects data should be collected is obvious if one remembers that operant behavior, which, of course, includes verbal behavior, can be altered through manipulation of the contingencies associated with that behavior. The formal properties of verbal behavior are maintained by social contingencies (e.g., Wolfert and Hayes 1988; Greenspoon 1955), and tight control over these contingencies is essential for generating replicable results.

The Addiction Research Center Inventory (ARCI), a frequently-used instrument for evaluating self-report of drug effects, was developed with the underlying hypothesis that different classes of abused drugs produce different spectra of self-reported effects. The resultant drug-related scales were empirically derived using prototypic drugs from each of the classes being categorized. Thus, there are sedative-related scales such as the Pentobarbital Chlorpromazine Alcohol Group (PCAG) Scale, stimulant scales such as the Benzedrine Group (BG) Scale, etc. There is, in addition, a composite drug effects scale, often referred to with the term "euphoria," (e.g., Jasinski et al., 1974) that seems to show increases with all drugs of abuse. Scores on the Morphine Benzedrine Group (MBG) Scale increase in a dose related fashion after administration of narcotic analgesics, barbiturates, or stimulant drugs. It has been suggested that to the extent that drugs produce this "euphoria" measured by the MBG scale of the ARCI, they will be abused "on the street." In fact, Jasinski et al. (1984) have stated that scores on a drug "liking" scale (Fraser et al., 1961) and "MBG scale scores are the hallmark subjective effects of abused drugs and define a drug as a euphoriant" (p. 197). Other drug rating scales have been developed or adapted from pre-existing scales, and have been used to measure self-reports in much the same way as the ARCI (e.g., Profile of Mood States, McNair 1971; "liking," de Wit et al., 1986).

These early studies evaluating drugs for abuse liability in humans did not measure the most salient feature of abuse -- the actual drug taking behavior. Screening drugs for abuse liability in laboratory animals, on the other hand, has concentrated on evaluating their ability to maintain responding leading to their delivery. The validity of such procedures is obvious; if we want to know something about a drug's potential to maintain self-administration, we can obtain the clearest data by studying that behavior. The development of a methodology utilizing chronically implanted

intravenous catheters for drug delivery over 20 years ago (Clark et al., 1961; Weeks 1962), and its utilization in the screening of many psychotropic compounds has demonstrated a good correspondence between those compounds self-administered by laboratory animals and those abused by humans (Johanson and Balster 1978). It is only relatively recently that we have begun to correlate these reinforcing properties of drugs with their discriminative stimulus properties, in either laboratory animals or human volunteer subjects (Bigelow and Preston, this volume).

Schuster and his colleagues (1981) surveyed the drug self-administration/ subjective drug effects literature for studies utilizing self-report ratings on the MBG scale of the ARCI to measure the effects of drugs that were also reported in the non-human self-administration literature. A review of the literature from 1970-76 indicated that it is often the case that drugs which readily serve as reinforcers in human and non-human research subjects also cause effects which lead to self-reports related to "euphoria." This, however, is not always the case, and it is the premise of this paper that these two actions of a drug can dissociate under a number of conditions. This will be discussed by utilizing data collected with stimulant drugs, specifically with cocaine. Cocaine is the example being used because although it is not a new drug, its effects were relatively unknown until recently, and it was only in the mid 1970s that we began to study its effects in humans.

LABORATORY RESEARCH

Single Dose Studies

Initial studies evaluated the physiological and behavioral effects of cocaine, attempting to correlate self-reported effects with cardiovascular changes, and relating these effects to cocaine plasma level. Normal healthy human volunteers, ranging in age from 21-45, and each with a history of cocaine use participated. Prior to acceptance in the study each volunteer passed an initial screening consisting of an extensive drug history interview, a psychiatric interview, and a complete physical examination. All of the subjects were admitted to an inpatient Clinical Research Center on the day prior to the first experimental session, where they were carefully monitored to insure that no drugs were taken other than those administered during the experimental session. Each subject signed a consent form which described the study, outlined the possible risks, and indicated that psychotropic drugs and/or saline would be administered, possibly on a daily basis, on all ten of the test days. When not participating in test sessions, subjects were free to engage in non-drug recreational activities of their own choice on the ward but were not allowed to leave the hospital. Subjects were tested individually, once daily, in experimental sessions

lasting 2.5 or 3.5 hours, and were monitored from an adjacent room. Subjects had intravenous lines inserted and were fitted with physiological recording equipment such as heart rate electrodes, a blood pressure cuff, and Manning bellows to measure respiration rate. Cocaine HCl dissolved in saline or physiological saline alone was injected over a 60 second period, and physiological measures were periodically collected. In addition, subjects answered two standard questionnaires before and repeatedly after drug or saline injection.

The Profile of Mood States (POMS) (McNair et al., 1971) is a 72 item 5-point adjective rating scale which yields scores on eight clusters: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation. Two derived scores were also used. Arousal scores were obtained by adding together the scores for Vigor and Anxiety and subtracting the scores for Confusion and Fatigue, and Positive Mood scores were obtained by subtracting the Depression from the Elation score. This version of the POMS has been described by Fischman and Schuster (1980). A second questionnaire was a short form of the 550-item ARCI (Haertzen 1966), consisting of 49 items compiled by Martin et al. (1971) which have been shown to be sensitive to the effects of a number of different stimulant drugs. The questions were taken from the Morphine Benzedrine Group (MBG) Scale, the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) Scale, the LSD Scale, the Benzedrine Group (BG) Scale, and the Amphetamine (A) Scale.

Early work with cocaine evaluated the drug as if it were an unknown compound, and initial single dose studies assessed its similarity to amphetamine (Fischman et al., 1976). It was assumed that similar profiles of action to a prototypic stimulant drug of abuse, amphetamine, might predict a similar abuse liability profile (Fischman 1977). The profile of cocaine's action in these initial intravenous studies indicated that cocaine is similar to *d*-amphetamine in both its cardiovascular and self-reported effects. Further, cocaine had measurable but not toxic effects in the 16-32 mg intravenous dose range, a dose range subjects rated as comparable to that they were taking outside of the laboratory.

Figure 1 presents heart rate data from nine subjects tested with single intravenous doses of cocaine. Heart rate increased significantly after 16 and 32 mg cocaine, peaking at 8-12 minutes after injection, and returning to baseline levels within 30-40 minutes. This decrease, seen also with self-reported data measured with the POMS and ARCI (Fischman et al., 1983b), parallels the decrease in cocaine blood levels seen after single doses (Javaid et al., 1978). These data are presented in figures 2 and 3.

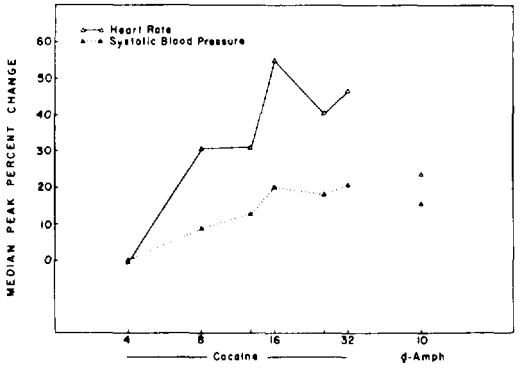

Figure 1: *Median percent change in heart rate for one hour after injection of saline or 4 to 32 mg cocaine. Percent change was calculated for each dose of cocaine with reference to its own 30-minute predrug baseline. Saline function representsdata collected on day 8 of experimental series; shaded area indicates the semi-interquartile range ofthosedata. (From Fischman et al., 1976, copyright 1976, American Medical Association.)*

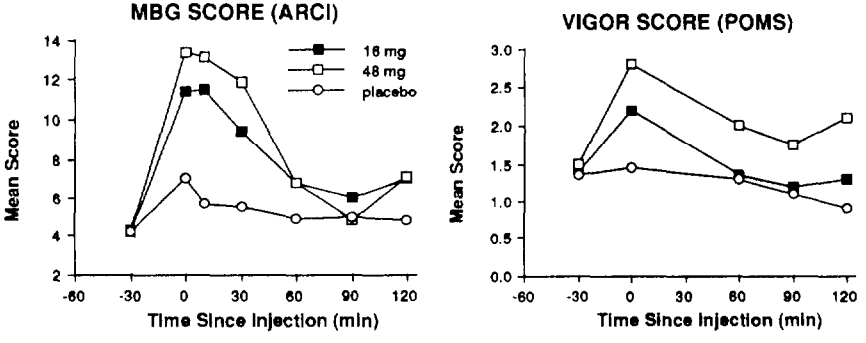

Figure 2: *Effects of a single dose of 16 or 48 mg cocaine or saline on scores of the MBG scale of the ARCI and the Vigor scale of the POMS. Data represent the mean of four subjects. (Data taken from Fischman et al., 1983b).*

In single doses, as with cardiovascular changes, there is a predictable increase in measures of variables such as Arousal, Vigor, and Friendliness, ratings of "high" (Fischman et al., 1983a, 1983b) and other stimulated- or "euphoria"-like reports such as the MBG scale of the ARCI, which peak at 5-10 minutes after i.v. injection, and generally begin to return to baseline within 30 to 60 minutes. Subjects state that they would be ready to take another dose of the drug during this 30 to 60 minute interval.

Interestingly, subjects were unable to differentiate between cocaine and d-amphetamine when the two drugs were administered under blind conditions, providing additional evidence for cocaine's comparability to amphetamine. These subjects were required to identify the drug received within the first 60 minutes after injection, and therefore were not able to discriminate on the basis of duration of effect. Further, subjects were given no training with the two drugs in question, relying only on their training outside of the laboratory, which was neither systematic nor necessarily accurate. Street drug is often cut with a variety of other substances, and frequently has low concentrations of the drug people believe they have purchased. It is likely, therefore, that subjects given discrimination training in the laboratory would be able to differentially respond to these two drugs.

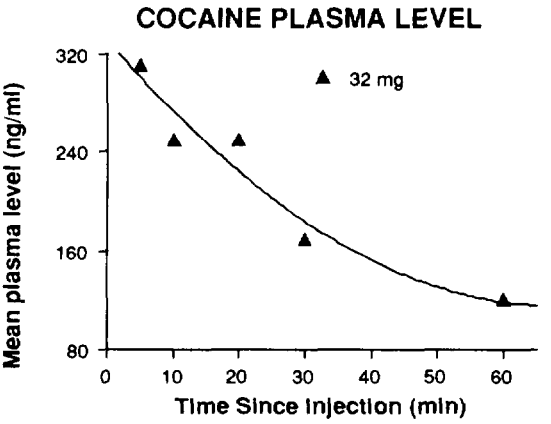

Figure 3: *Mean cocaine plasma level for 10 subjects administered 32 mg intravenous cocaine. (Data taken from Javaid et al., 1978).*

The profile of cocaine's action in the single dose intravenous studies suggested that cocaine had high abuse liability - rapid onset of action with major subjective effects at doses that singly had relatively small physiological effects, and a reasonably short duration of action. A short duration of action that allows for repeated dosing provides repeated opportunities for the initial rapid drug onset, or "rush," which experienced users claim is the "best part" of the drug's effect. Under this single dose paradigm, it is clear that self-reported "positive" effects (i.e., stimulant-like) indicate that cocaine has a significant abuse liability. Epidemiological studies have recently verified that cocaine and the amphetamines are extensively used and abused (see review by Fischman 1987).

Self-Administration Studies

Although the single dose paradigm with drug administered by the experimenter is a useful procedure for evaluating profile of action, including toxicity, it provides little information about the effects of the drug when it is relatively freely available and users can take it as they would outside of the laboratory. The next step in evaluating cocaine's

abuse liability therefore, was to develop a self-administration procedure which could provide information about patterns of intake and the effects of the drug when taken under subject-controlled administration conditions. In this manner the physiological and self-reported effects of cocaine could be compared to blood levels engendered during cocaine self-administration. The procedure developed here was adapted from that developed by Johanson et al. (1975) to test drug choice in rhesus monkeys.

Normal healthy volunteer subjects with histories of cocaine use participated for 2 weeks in daily experimental sessions lasting 2-3 hours (Fischman and Rachlinski 1989). During each experimental session subjects sat in a comfortable reclining chair facing a CRT screen and a response console containing a computer keyboard and three 1.7 x 1.7 mm touch sensitive plates. Thirty minutes prior to the daily test session, each subject had two Minicath infusion sets inserted, one into each arm. As in earlier studies, these were connected via extension tubing to bags of 0.9 percent physiological saline which was slowly dripped in order to maintain the patency of the intravenous connection. Drug or saline was injected through one catheter, and the other was used to withdraw blood for later cocaine blood level analysis (see Javaid et al., 1983). Each test session consisted of a 30-minute pre-drug baseline recording period followed by a 1- or 2-hour drug choice session. Physiological and behavioral measures were taken repeatedly during each test session. All subjects were monitored for 1 hour after the end of the choice session.

During the 30 minutes immediately preceding the beginning of each choice session, baseline electrocardiogram (ECG) and blood pressure measures were collected, and a series of questionnaires was presented on the CRT in front of them, one item at a time, paced by the subject's responses on the computer keyboard. These questionnaires included the POMS and the ARCI as well as a set of Visual Analog Scales, which consisted of six 10 cm lines, presented one at a time, labeled "not at all" on the left side and "extremely" on the right side of the screen. The lines were labeled consecutively "stimulated," "high," "anxious," "sedated," "down," and "hungry." Subjects could indicate how they felt in relation to each descriptive adjective by moving the cursor to a specific place on each line.

Subjects were given a choice between cocaine (4, 8, 16 or 32 mg) and saline or between two doses of cocaine periodically during each test session. They were told that one solution (solution A or solution B) would be associated with the left touch plate on the console in front of them, and a second solution (solution A or solution B) would be associated with the right touch plate. Although the drug/position association would hold within a daily test session, it could vary between test sessions. Solution A was always a cocaine dose; solution B was a lower dose of cocaine or

saline. Subjects could choose an intravenous injection by tapping on one of the two touch plates, with the first tap indicating an irreversible choice and the required number of taps varying from 10 to 200. When the response requirement was completed, the questionnaires were presented, one item at a time on the CRT. After completion of these, which took approximately 4 minutes, a blood sample was taken for cocaine blood level analysis, and the chosen solution was injected over a 1 minute period. In some studies another drug choice was again immediately available, while in other studies a timeout, during which no drug was available, was inserted between each drug choice trial.

Subjects reliably chose cocaine in doses of 4, 8, 16 and 32 mg/injection over saline. This was true whether the response cost for an injection was 10 responses or 200 responses. They also chose 32 mg cocaine over 16 mg. Interestingly, in the single dose studies described above, subjects rated the 16 and 32 mg doses comparably, and somewhat larger than the average dose of stimulant they were accustomed to taking outside of the laboratory (Fischman et al., 1976). In addition, no self-reporteddifferences between 16 and 32 mg were obtained using the ARCI or the POMS. In the present self-administration study, 16 and 32 mg injections of cocaine also engendered similar profiles of self-reported effects. Only scores on the LSD scale of the ARCI and the Anxiety, Vigor, and Arousal scales of the POMS revealed significant differences between these two doses. It is important to note that, despite similarities in the self-reported effects of these two doses, when allowed to choose between them, subjects showed a clear preference for the higher dose.

Subjects self-administered cocaine in a regular pattern, spacing injections every 6-10 minutes during the one hour session, when no timeout occurred. Figure 4 presents data from a single subject (#50) on day 6 of a study in which the choice was between 32 mg and saline. This subject chose 32 mg on all six of the choices she made, with cocaine plasma levels reaching 1100 ng/ml. Regular rates of cocaine intake have also been reported for non-human research subjects with lever pressing maintained by injections of cocaine (Johanson 1980). This subject showed a maximal heart rate after the initial dose of 32 mg cocaine, when heart rate, 55 beats/min prior to cocaine, reached 80 beats/min. This represents a 45 percent increase in heart rate 8 minutes after intravenous injection of 32 mg cocaine. Plasma levels of cocaine were approximately 540 ng/ml at this time.

Heart rate remained around 70 beats/min, a 27 percent increase above baseline, until approximately 20 minutes after the start of the session, prior to the third cocaine injection. After that, despite an increase in plasma level from 710 ng/ml to 1100 ng/ml over the remaining portion of the session, heart rate returned to levels that were 10-12 percent of baseline, and within the range of variability for this subject. MBG scores

session and just prior to the third dose of cocaine administered. MBG scores remained level or decreased after this, falling to a low of eight by the end of the session.

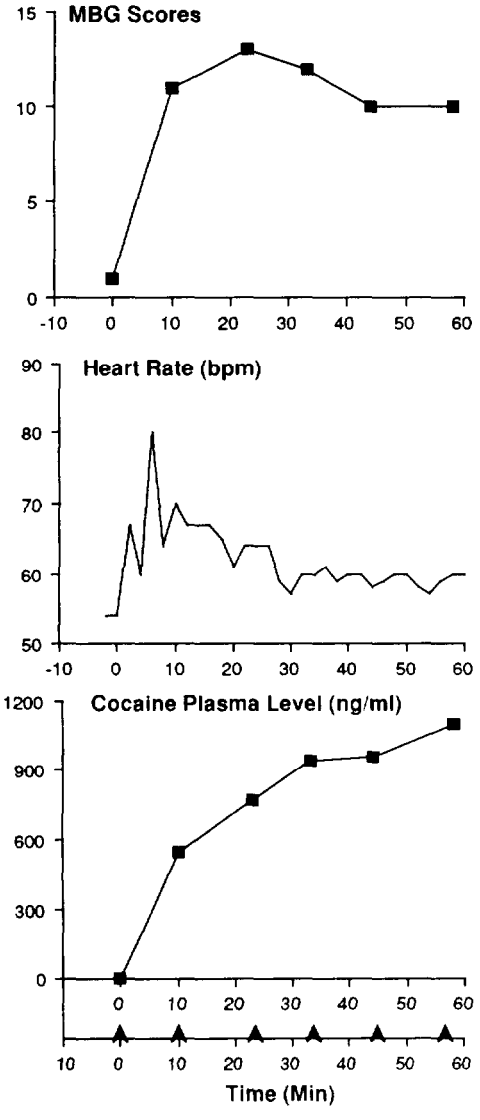

Figure 4: *Data from Subject #50 give the choice between saline and 32 mg cocaine Arrows represent choices of 32 mg cocaine. Cocaine plasma levels, heart rate and MBG scores are presented for thar session.*

Subjects'reports of cocaine's effects during this self-administration procedure were generally similar to those obtained with other stimulant drugs (Martin et al., 1971) and with other drug administration procedures (e.g., Fischman, et al., 1976, 1983 a,b). There were increases on the BG, MBG and LSD scales, as were also reported for a number of other psychomotor stimulant drugs (Martin et al., 1971) and for cocaine (Fischman, et al., 1976).

POMS data also reflected the similarity between cocaine and other psychomotor stimulants in the self-report data engendered. Johanson and her colleagues (Johanson and Uhlenhuth 1980; de Wit et al., 1986), studying the effects of oral drug, have generally found increases in Vigor, Confusion, Elation, Arousal and Positive Mood scores as well as decreases in Fatigue scores after amphetamine as well as phenmetrazine (Chait et al., 1985). Sixteen and 32 mg cocaine similarly caused increases in those scores as well as additional scales such as Anxiety and Friendliness. The route of administration probably accounts for this increased sensitivity of the current procedure.

Of particular interest in the current study were the differential effects of the lower doses of cocaine and saline on drug self-administration. This was especially evident when the response cost for an intravenous injection was raised to 200 responses. Subjects reliably chose 8 mg cocaine over 4 mg, and both doses were reliably chosen over saline. Neither self-report data nor cardiovascular measures indicated any differential effects of these lower intravenous doses. Subjects continued to self-administer 4 mg even when a timeout was introduced between drug choices. The "euphorigenic" effects of the self-administered drug, generally assumed to be a major determinant of abuse liability (Jasinski et al., 1984), appear not to be necessary to predict cocaine's reinforcing function. This dissociation between the verbal report data and the self-administration data provides important evidence for the sensitivity of this choice paradigm.

Figure 5 presents mean scores on the MBG scale during cocaine choice sessions. These scores increased significantly ($p<0.01$) and remained elevated through the first few injections of 16 mg and 32 mg cocaine, but then decreased even though plasma cocaine concentration continued to rise during repeated cocaine injections. The data presented here do not represent a ceiling effect. The maximal score for this scale is 16, and mean scores of 13.9 have been reported after single intravenous doses of 48 mg cocaine (Fischman et al., 1983b). Similar inverted u-shaped curves were collected for reports of feeling "high" and "stimulated." An example of the self-reported effects data collected during a single session are presented in figure 4, where MBG scores peaked at 13, a considerably larger score than the mean shown in figure 5. The data from this single subject during a single session are quite similar in shape to the mean data presented in figure 5.

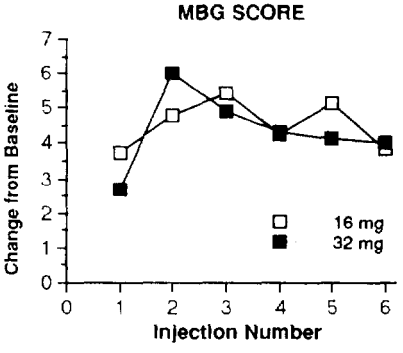

Figure 5: *The effects of repeated doses of 16 or 32 mg cocaine on the MBG scale of the ARCI. Mean change from base-line scores are presented after each injection of 16 or 32 mg cocaine. (Taken from Fischman and Rachlinski, submitted,* 1989.)

These data point to the development of tolerance within a single session. The development of acute tolerance, defined as a decrease in responsiveness to cocaine within a single session, was also reported to occur when a single intravenous injection of cocaine was administered 1 hour after subjects were allowed to inhale 96 mg of cocaine powder (Fischman et al., 1985). When self-administered repeatedly within a

session, 16 and 32 mg exerted maximal and significant cardiovascular and self-reported effects following the first injection, with subsequent injections exerting smaller or no effects. This was true despite a steadily increasing cocaine plasma level, achieving peaks of almost 1000 ng/ml following the final injection. Subjects exhibited no residual tolerance to the self-reported effects of cocaine 22 hours later, when the next test session was carried out. Neither baseline levels nor response to the initial dose of cocaine were influenced by the previous day's dosing regimen. This was the case for both the two dose experimenter-initiated regimen (Fischman et al., 1985) and for the repeated dose self-administration paradigm (Fischman and Rachlinski 1989).

Cocaine caused increases in heart rate comparable to those reported in other studies evaluating the effects of this drug administered intravenously (Fischman et al., 1976, 1985). As with most of the self-report measures, 16 and 32 mg did not produce signicantly different effects on heart rate although 8 and 16 mg did. The effects of repeated injections of 4 mg cocaine were no different than repeated injections of saline. Heart rate changes paralleled those measured on most of the self-report questionnaire scales. Maximal effects were measured after the second injection of 8, 16 or 32 mg cocaine, with no further increases seen. As with the verbal report data, these results do not represent a ceiling effect. For example, mean heart rate for the first 6 minutes after the second injection of 16 mg averaged 95 beats per minute, a significant increase from the mean baseline of 74 beats per minute, but clearly below maximal levels. Peak heart rates after this injection reached 120-135 beats per minute for some subjects while for others they remained below 100 beats per minute. The data clearly indicate a decrease in cocaine's heart rate increasing effects when repeated doses are administered within a relatively short period of time. These effects are also shown, in figure 4, for a single subject.

Ambre et al., (1988) carefully demonstrated acute tolerance to the heart rate increasing effects of cocaine using a constant intravenous cocaine infusion to maintain a steady state cocaine plasma level for 4 hours. Tolerance to the chronotropic effect was incomplete, however, since heart rate remained stable but elevated above baseline levels. Rating of "high," however, declined to baseline by approximately 270 minutes after the onset of cocaine administration. Kumor et al. (1988), on the other hand, reported little evidence of tolerance development to cocaine's heart rate- and blood pressure-increasing effects in subjects maintained at a stable blood level. It is possible, however, that the drop in heart rate and blood pressure they reported after 15 minutes might represent a partial development of acute tolerance. The data from a number of studies (Fischman et al., 1985, 1989; Foltin et al., 1989; Ambre et al., 1988) thus are generally supportive of the development of an acute tolerance to

cocaine's effects, some of which were collected under self-administration conditions comparable to those seen outside of the laboratory. Acute tolerance development might be an important factor for those who "binge" on cocaine.

Generalization to Other Drugs

Cocaine is not simply another amphetamine. It is, in fact, a local anesthetic with stimulant properties, and it is logical to ask whether its local anesthetic properties affect cocaine's profile of effects. For example, do these qualities contribute to its reinforcing effectiveness? Data from the animal laboratory have shown that at least some of the synthetic local anestheticscanmaintain self-administration in non-human research subjects (Ford and Balster 1977; Hammerbeck and Mitchell 1978; Johanson 1980). The data on local anesthetic self-administration in non-humans have been puzzling since, in general, drugs which serve as reinforcers in animals do so in humans, and it is assumed that this property of reinforcing effectiveness is an important factor for a drug's dependence potential. Despite these reports of local anesthetic self-administration in non-humans, however, they do not appear to be commonly abused by humans.

We used the same general approach in collecting abuse liability information about the local anesthetics that we did with cocaine. Volunteer subjects were tested with a range of intravenous doses of one drug, procaine, from the group of those self-administered by monkeys, and one drug, lidocaine, from the group of those that were not self-administered (Fischman et al., 1983a,b). The effects of these two drugs were compared to those of cocaine, a local anesthetic with substantial abuse potential. We were particularly interested in the profile of self-reported effects engendered by these drugs, as self-report profiles have been related to abuse potential in the past.

Matched intravenous doses (16, 32, and 48 mg) of cocaine, procaine and lidocaine were administered, one dose per day, in a balanced order, and physiological and self-reported effects of these three drugs weremeasured. In addition, subjects were asked to identify the drug they were administered each day, choosing among "placebo,""cocaine," or "other." Only cocaine had significant cardiovascular effects, causing dose-related increases in heart rate and blood pressure. Lidocaine produced no consistent effects on self-report questionnaires, and all doses were identified as "placebo." Apreviousstudy, however, reported that cocaine and lidocaine engendered similar ratings of "high" when these two drugs were topically administered in solution intranasally in matched doses of 0.19, 0.38 and 0.75 mg/kg (Van Dyck et al., 1979). However, in that study, no statistical analysis of the data were reported, and it was likely that cocaine's effects were not significantly different from placebo (see Fischman 1984). The similarity

between cocaine and lidocaine on ratings of "high" in the study by Van Dyck et al. (1979) may have been the result of the absence of any drug effect, as might be anticipated given the low doses of cocaine tested. In the present study no dose of procaine produced self-reported effects different from placebo, excepting that subjects identified the 48 mg dose of procaine as cocaine. Assuming that the 48 mg dose might have been a threshold dose of procaine, 96 mg procaine was also administered, and it too was identified as cocaine. In addition, although there were no significant effects of either dose on responses on the POMS or ARCI, 96 mg procaine caused a significant increase in scores on the "high" and "stimulated" scales.

These data indicate that procaine and cocaine share some stimulus properties, not including cardiovascular changes or effects measured by the POMS and ARCI, but perhaps including the potential stimulus cues measured by the "high" and "stimulated" responses, cues shared by many drugs. To the extent that changes in "high" and "stimulated" suggest a possible reinforcing function this implies that procaine might be expected to function as a reinforcer in humans. The next study directly investigated this possibility by allowing subjects to self-administer procaine or lidocaine using the choice paradigm (Fischman 1981).

No subject self-administered lidocaine at greater than chance levels. As has been shown with rhesus monkeys, lidocaine does not maintain responding leading to its administration. As with the rhesus monkeys, however, procaine did maintain responding (Johanson 1980; Woolverton and Balster 1982). All subjects chose 48 mg intravenous procaine over saline on at least 75 percent of their choices, but when subjects were allowed to choose between 8 mg cocaine and 48 mg procaine, all subjects chose the cocaine. Eight mg of cocaine was also reliably chosen over 96 mg procaine.

It appears that cocaine and procaine have some overlapping stimulus properties which do not include heart rate changes, nor scores on several standard questionnaires, but do include something classified by subjects in the category of "getting high." Clinical data also suggest that procaine infusions are often accompanied by reports of mood changes in patients (Ostfeld et al., 1977; Zung et al., 1974). Despite these similarities, procaine is not thought to be abused by humans. This discrepancy could be due to several factors. First of all, it has a short duration of action, with an elimination half life of approximately 8 minutes compared with a 40-60 minute half-life for cocaine. A very short duration of action requires frequent injection, which is inconvenient for humans to arrange. Potency differences are also relevant. There appears to be a 6-10 fold potency differential between cocaine and procaine when the animal self-

administration and discriminative stimulus property data are examined (Woolverton and Balster 1982). The need for both frequent injections and substantial amounts of drug might well be a reason for its lack of street use. Secondly, it is possible that procaine is a reinforcer and is being used on the street in its own right. Procaine is commonly misrepresented as cocaine or mixed with the cocaine that is sold on the street (Hammerbeck and Mitchell 1978). It has also been described as used to cut heroin. This may be a situation in which the presumably inactive substance used as filler is not, in fact, inactive.

Drug Interactions

If self-reported drug effects provide information which can predict abuse liability, it should be possible to shift these verbal reports of cocaine's effects with a drug which is useful as a pharmacological intervention in treating cocaine abusers. Kleber and his colleagues have reported that cocaine abusers who are administered desipramine and maintained in behavioral treatment remain in treatment and are abstinent significantly more than those given only the behavioral treatment (Gawin and Kleber 1984).

Seven normal healthy volunteer subjects were tested daily and given the opportunity to self-administer doses of cocaine or saline approximately once every 12 minutes to a maximum of seven injections within a 90 minute period (Fischman and Foltin 1988). As with the choice study described above, subjects could choose saline or a dose of cocaine by responding on the left or right lever. The lever associated with cocaine or saline remained constant within a day, but could change from day-to-day.

Sessions began with a 30 minute baseline period. Stimulus lights signalled the availability of a drug choice, and the initial response on one of two levers indicated an irreversible choice. Next, 200 responses were followed by injection of the chosen solution, if medically indicated. Finally the self-report drug effects questionnaires were presented and blood was occasionally withdrawn for cocaine levels.

Seven choice opportunities were presented during a typical session. The self-administration protocols were carried out over a 14-day interval while subjects resided in the hospital. A 3-4 week desipramine outpatient maintenance period was then carried out. During this period subjects reported to the laboratory daily, and bloods were withdrawn to monitor desipramine blood levels twice weekly. Blood levels were maintained at approximately 125 ng/ml during the remainder of the study. After the outpatient desipramine maintenance period, subjects were returned to the hospital and a second 14-day choice phase was begun with desipramine blood levels maintained at approximately 125 ng/ml.

Desipramine had no effect on cocaine-taking behavior, with a mean of approximately six injections requested during sessions in which cocaine was available. Response rates and latency to first response were also unchanged. We were, however, not always able to administer the injections requested because of medical considerations (i.e., diastolic blood pressure above 100 mg Hg or heart rate above 131 bpm), and this was more generally related to the desipramine maintenance. Thus, fewer cocaine injections were administered during desipramine maintenance.

Decreases in cocaine craving have been anecdotally reported for cocaine abusers being treated with desipramine. In an effort to operationalize "craving" a visual analog scale labeled "I want cocaine" was administered as part of the battery of self-report questionnaires answered repeatedly during each session. Before desipramine maintenance, subject's scores on this scale were close to the maximum of 100. During desipramine maintenance, scores on this scale were substantially and significantly lower.

Cocaine's stimulus properties were evaluated through the use of self-reported drug effects. As discussed above, a number of self-report scales are reliably increased after administration of cocaine and other psychomotor stimulant drugs. Desipramine had the effect of attenuating scores on many of the stimulant-related scales including Arousal, Positive Mood and Vigor on the POMS, and BG and MBG on the ARCI. Prior to desipramine maintenance, these scores were increased by the initial dose of cocaine in a dose-related fashion. Such effects have been found previously for cocaine as well as for other psychomotor stimulant drugs, such as amphetamine (Fischman and Rachlinski 1989; Johanson and Uhlenhuth 1981). During desipramine maintenance, cocaine engendered significantly lower scores on these scales.

A second pattern of effects on other self-report scales was also evident. Desipramine maintenance resulted in lower placebo scores and significantly higher scores in response to cocaine on the Confusion and Anger scales of the POMS and the ARCI LSD scale, a measure of dysphoric drug effects.

Although desipramine maintenance, under these controlled laboratory conditions, does not appear to affect cocaine self-administration, it does appear to modify some of cocaine's subjective effects as reported by our subjects. It is possible that, in a more elaborate choice paradigm, desipramine-induced changes in the reinforcing effectiveness of cocaine might be identified, perhaps by allowing subjects to choose another reinforcer in preference to cocaine. If such a change does, in fact, occur, desipramine maintenance of cocaine abusers might make it possible for them to learn to respond to other stimuli in the environment, thereby

engendering something other than cocaine-seeking or cocaine-taking behavior. The data we have collected are consistent with such a hypothesis.

CONCLUSIONS

The data discussed in this paper suggest a generally good correlation between cocaine self-administration and its stimulant-related, "positive" effects. There are, however, areas in which these two measures clearly diverge, and these areas provide interesting topics for future research. It is clear that the laboratory self-administration model provides a sensitive paradigm for detecting those drugs which can maintain behavior leading to their delivery. Changing the response requirement for a drug injection increases the likelihood that small differences in dose will become more relevant in determining drug choice. However, it is possible that under these conditions subjects will work to self-administer drug, no matter how small the dose. They will, on the other hand, often stop responding when saline is their only choice, as we recently showed in the desipramine maintenance study. It is possible that laboratory conditions provide cues for drug-taking which do not exist outside of the laboratory. Thus, although the choice self-administration model appears to be generally valid for the identificationofreinforcingeffectiveness, itmightnoteffectively address relative reinforcing effectiveness because no other reinforcers are competing and no other behavior is required. Bigelow et al. (1974, 1975), for example, manipulated contingencies such as social variables and showed that they could have an effect on drug self-administration. What would happen in these cocaine self-administration studies, for example, if drug self-administration had an effect on earning power, decreasing it slightly? We know, for example, that subjects required to perform a simple learning task show increased cardiovascular responsivity as evidenced by increased heart rate and blood pressure during the time they are performing the task (Capriotti et al, 1988; Foltin et al, 1988). Cocaine also increases heart rate and blood pressure. The two in combination cause even greater increases, and when alcohol is added to this paradigm, mean heart rates in excess of 60 percent of baseline have been measured (Fischman and Foltin 1988). Unfortunately, there are no data available on cocaine self-administration when subjects also have to perform tasks in order to earn money, nor on self administration when subjects are consuming other substances as well. These might be necessary to better predict the conditions under which subjects take cocaine outside of the laboratory.

The relationship between drug self-administration and self-reported effects of the drug being administered appears to be complex, with self-reports providing partial predictive power about the abuse liability of any drug.

It is clear, however, that they do not substitute for measuring the actual drug taking behavior, and in the absence of a good measure of the drug taking behavior we cannot be certain about whether a drug will support self-administration, or about the conditions under which self-administration will occur. It is only by evaluating these effects within a behavioral context that we can fully understand and predict abuse liability.

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CHAPTER 11

Case Reports and the Assessment of Drug Abuse Liability

Edward C. Senay, M.D

INTRODUCTION

The focus of this paper is on unsolicited, unstructured case reports in Phase 4 of new drug development. Formal case reports as a part of Phase 2 and 3 are not considered. As far as I am aware, formal case reports in Phase 2 or 3 have not, to date, incorporated scales for detecting addictive behavior patterns even simply considered as a category of non-occurrence. Pocock (1983) speaks of "Phase 4 trials" as "promotion exercises aimed at bringing a new drug to the attention of a large number of clinicians, typically in general practice." Pocock states: "This latter type of inquiry has limited scientific value and hence should not be considered part of clinical trial research." I cannot agree with this position with respect to potential for abuse liability, a term which I will sometimes use to indicate both potential for inducing physical dependence and abuse liability, more narrowly defined. History appears to teach that both science and an extended non-scientific experience are necessary before we begin to appreciate the true profile of the abuse liability of a new psychoactive drug. The basic argument of this paper is that, to date, unsolicited, unstructured case reports have been the single most important means of detecting abuse liability.

Case reports in this paper refer to either Phase 4 clinical trials as defined by Pocock or to the much more important part of Phase 4 - the ordinary clinical encounter between doctor and patient which is either transmitted to an authority such as the Food and Drug Administration (FDA) or perhaps toajoumal. The case report I want to focus on is usually unsolicited and it is not structured as a formal case report would be in Phase 2 or 3. The clinicians Phase 4 case report usually does not cover the full range of possible symptoms as would a structured Phase 2 or 3 report and, in particular, the clinicians report is often lacking in the category of non-occurrence.

Case reports, in Phase 4, are the vehicle for completing the book, so to speak, on a given drug for it is in this Phase that some drug effects, usually negative, are appreciated which were not apparent in previous phases of drug development. The conditions in Phase 4 are natural; no blinds are utilized; psychological factors related to status of assignment to drug or placebo are not present and usual clinical conditions prevail. It is also important to remember that in Phase 4 both clinician and patient usually believe that the drug is safe as the authorities have placed their imprimatur on the drug.

Phase 4 experience involves most or all of the relevant cases which might be appropriate for the drug in question with no artificial testing induced boundaries and also, as in the use of benzodiazepines for relief of ordinary life stress, we acquire experience with non-indicated uses. Phase 4 case reports then are the final detection line for all the potentials of a drug including indications for which it has been developed and for many, perhaps, unanticipated indications and problems including abuse liability.

With respect to potential for abuse liability, Phase 4 studies may have to involve truly enormous numbers of patients before the true profile of a drug is revealed. The benzodiazepines are the most recent example, for it was not until these drugs had been used in tens of millions of cases that their potentials for abuse liability were appreciated. Unsolicited and unstructured case reports were the vehicle by which these potentials were first detected. The importance of Phase 4 is underscored by the fact that after 28 years and use in billions of instances we still do not have a complete profile of the potential for abuse liability of this class of drugs. For example, we do not know with scientific certainty that all members of this class have equal potential for inducing physical dependence although the preponderance of current evidence indicates that all members of this class are equal in this respect.

LIMITATION OF CASE REPORTS

After citing the importance of case reports in the long process of appreciating the abuse liability of a psychoactive drug it is important to understand that there appears to be a spectrum underlying ordinary clinical experience. One end of this spectrum is defined by very clear reporting which is congruent with evidence derived from scientific study. The other end of this spectrum is defined by reports which are not congruent with scientific evidence and which appear to have more to do with the need of people to find some meaning in existence than with pharmacology. I will start in the middle of this spectrum.

Any clinician can see only a small fraction of the extant cases of a given disorder and, therefore, may not see much of the variance

Benzodiazepines were used in millions if not billions of instances over a period of some twenty years before there was general recognition in the medical and scientific community of the potential of these drugs for inducing physical dependence (Marks 1985). If, as now appears to be an incontrovertible fact, these drugs can induce physical dependence in ordinary doses for relatively brief periods e.g., 4 months of daily doses, how could this propensity have gone unnoticed for close to 20 years of massive use? One factor of probable relevance is that most clinicians see a variety of patients and, in many instances, for brief periods of time. Even clinicians, like myself, who see a narrow spectrum of patients can have only a very limited exposure to the total group of patients, for whom we provide services. For example, over a 20 year span I estimate that I have admitted to treatment an average of ten heroin addicts per week for approximately 4.5 weeks each year. Mathematically, then, I have been exposed to 9,000 patients. If there are 750,000 to one million addicts in the U.S. alone then I have been exposed to a small fraction of the world's heroin addicts. Even groups of clinicians cannot be exposed to substantial fractions of problems like substance abuse disorders which have a lifetime prevalence of 15 percent in the entire population of the U.S. and a somewhat lesser but still substantial prevalence in many countries in the rest of the world.

Placebo effects: "expectation" and drug fads

"Expectation" and the limits of clinical sensitivity: Clinical observation is, of course, confounded by a number of factors of which placebo effects are quite powerful. Beecher cited a figure of 30 percent placebo effect for the analgesic properties of morphine (Beecher 1955). The average clinician probably does not appreciate the power of this effect for it is almost always hidden in ordinary clinical life and the average clinician has other things to occupy his or her attention. The significant contribution of "expectation" to variance in opioid withdrawal was demonstrated in a double blind study we carried out in which complaints of narcotic withdrawal did not differ between groups of addicts being withdrawn and a group of addicts not being withdrawn (Senay et al., 1977). "Expectation" resulted in no differences in complaints but a second factor, namely, rate of withdrawal caused large differences in behavior as those being withdrawn at a rapid rate used more heroin and dropped out of the study at significantly higher rates than groups being withdrawn at slower rates or not being withdrawn at all. The culture of heroin addiction pays respect

to the contribution of "expectation" as many addicts will volunteer that the "headtrip" aspect of withdrawal is important, but neither addicts nor acute clinical observers would be able to separate out effects on complaining versus those on behavior. There is a boundary on clinical sensitivity, and detection of effects beyond that boundary requires scientific method.

The limits of both clinical sensitivity and scientific method can be seen in the following. It is a common clinical experience to encounter a patient who is so frightened of withdrawal from a drug of dependence that their fear takes on phobic proportions. They are literally unable to think about participating in a withdrawal program. One usually advises and obtains consent for a blind detoxification. But the clinician cannot separate expressions of the phobia about withdrawal from pharmacologically induced withdrawal effects. Covi et al. (1973) tried to combine scientific method with an individual case report when he hospitalized a patient who had taken chlordiazepoxide 45 mg daily for 20 weeks. Under double blind conditions the chlordiazepoxide was abruptly discontinued, but Covi could not determine if the resulting syndrome was attributable to withdrawal, to a return of symptoms for which the patient had originally been treated or to a phobia about withdrawal.

Drug fads and drug reputations: Another factor which confounds ordinary clinical experience is that of drug fads - attribution of desirable effects to a drug which have nothing to do with its pharmacologic effects or drug reputations - attribution of undesirable effects which again have nothing to do with the pharmacology of the drug. First, I would like to examine drugs which are what they are said to be. Methadone, for example, has long been said by addicts to "get in your bones." There is no scientific evidence for such an effect. The most probable explanation is that many addicts in methadone maintenance treatment in attempting to withdraw from methadone experience narcotic withdrawal which is moderate to severe in degree. Bone aches are prominent in these degrees of severity and are not prominent in mild degrees of withdrawal. "On the street" many addicts never obtain enough heroin to experience such degrees of severity of withdrawal, hence the attribution of bone aches to the methadone. Another illustration of drug reputations was evidenced in the early work with 1-alpha-acetyl-methadol; patient acceptance of the drug was trouble free in most centers experimenting with the drug but in one center the drug was "bad-rapped" and the experimenters could not get any addicts to accept the drug.

In the late seventies in Chicago the combination of tripelennamine and pentazocine, so-called "T's and Blues," largely replaced heroin in

confirmed, hard-core heroin addicts (Senay 1985). Rational reasons for thechangewere: 1) low cost, a "set" of "T's and Blues" could be purchased for 5 dollars and a potent dose of heroin cost around 20 dollars and 2) certainty, with "T's and Blues" addicts knew that they were going to get potent drugs; addicts reported that heroin purchases were entirely unreliable hence the shift to "T's and Blues." Fad aspects of the "T's and Blues" phenomena were in evidence when many addicts maintained that intravenous use of "T's and Blues" would relieve heroin withdrawal. In the general hospital I have seen more than one heroin addict, who concealed the fact of his addiction, thrown into severe narcotic withdrawal when he received pentazocine for post-operative analgesia and so believe that pentazocine is indeed a potent narcotic antagonist when given to someone with true physical dependence on opioids. Many addicts in my clinic, however, steadfastly maintained that "T's and Blues" would "take their sick off." Their "sick" i.e., their withdrawal, was most likely placebo effect withdrawal of the kind discussed above and would yield to any intervention in which the addict had strong belief.

The inclusion of a small amount of naloxone in the pentazocine capsule together with a new shape and color combined to end rather dramatically the "T's and Blues" epidemic in Chicago. A few addicts stayed away from "bananas" or "footballs", as the new formulation came to be known on the street, because shooting them led to severe narcotic withdrawal, but most addicts reported that they gave up on the new form of Talwin because the new drug didn't seem to have any intoxicating effect. As one of them said to me, "footballs don't have any drive to them." There were also fears that the new form of Talwin had destructive effects on sexual function and that hallucinations were more likely with the new drug. Probably such fears motivated a return to heroin for some addicts, but the reports of most of the addicts who had experimented with the new formulation did not seem to confirm such effects. There were dramatic changes in the perception of Talwin and as one who witnessed the birth, growth and death of the T's and Blues epidemic in Chicago, I believe that changes in perception were as potent as pharmacologic factors related to the inclusion of the naloxone in the rapid demise of an epidemic which had lasted for many years.

Another illustration of placebo or "fad" phenomena is in the epidemic use of antidepressants among heroin addicts in New York City in the late seventies. Street lore attributed enhanced intoxicating qualities to the combination of tricyclic antidepressants and opioids and use to "boost" intoxication from heroin or methadone became quite frequent. The following table contains data on methadone maintenance patients and the drugs they were using (Kaul and Davidow 1981). One notes that use of

antidepressants as adjunctive drugs was more frequent than use of heroin in 1977-79 in the methadone maintenance patients studied in New York City. It is likely that most of these addicts had a choice and elected the antidepressants in preference to heroin. It is striking that rates of adjunctive use of tricyclic antidepressants were not far from those obtained for cocaine. Tricyclic antidepressants are abused in Chicago and in other communities, but on an occasional basis, and they do not rival the popularity of heroin or cocaine.

Table 1. Relative incidence of various abused drugs among methadone patients' as determined by immunoassay techniques[2,3].

	Percent positives					
Drugs	1974	1975	1976	1977	1978	1979
Cocaine	7.4	17.6	17.8	19.4	26.3	26.0
Heroin (opiates)	14.2	14.2	10.4	7.9	13.6	13.9
Barbiturates	7.8	8.8	14.6	5.2	10.5	10.0
Amphetamines	4.4	3.2	6.2	5.5	13.2	13.2
Tricyclic antidepressants	ANA	ANA	ANA	15.4	18.4	19.0
Benzodiazepines	ANA	ANA	ANA	11.2	14.9	17.3
Phencyclidine(PCP)	ANA	ANA	ANA	ANA	10.2	10.8

[1] Range of sampling in any given year was from 1,000 to 7,500 random patients screened.
[2] RIA and EMIT methodology.
[3] ANA = assay not available (developed) at the time.
(Permission to reprint from Kaul & Davidow, 1981 by Marcel Dekker, Inc.)

It is possible that heroin addicts in New York City know something about the pharmacological interaction between tricyclic antidepressants and opioids that addicts in other cities do not know but the preponderance of evidence available at this time suggests a drug fad. Kaul and Davidow write, "The concurrent use of 2 or more drugs is usually governed by the need for mood changes required at any given time. Substitution of one drug of choice for another is not necessarily the trend among drug users. They will add other drugs to their armamentarium for kicks."

Next I would like to review drug fads and drug reputations when the drug believed to be ingested is probably not the drug the taker believes it to be. In Chicago we witnessed a near epidemic of "THC" or as it was also called "TAC." The acronym "THC" was taken from tetra-hydrocannabinol. Street usage rapidly made THC into TAC or TIC, and it was a popular drug with non-heroin drug using youth in Chicago. The

drug "TAC" sold as "the essence of marijuana" was, of course, phencyclidine. The usual street report was that TAC gave a marijuana high but stronger than that associated with the usual street "'joint." It is quite possible that marijuana and phencyclidine have similar intoxicating properties, particularly at lower doses, but it is equally plausible that placebo effects accounted for the identification of phencyclidine as marijuana.

Two examples from the useful end of the spectrum of clinical reporting: For usual clinical purposes reports from heroin addicts on admission to treatment are accurate enough to make good estimates on first dose of methadone; a dose which may differ by 20 to 25 mg depending on the history. We studied 220 addicts coming into treatment and administered placebo or 10 mg of methadone and took baseline and 2 hour pupillary photographs under controlled light conditions (Senay and Schick 1978). Following a dose of 10 mg of methadone, all normals will have a pupillary constriction of 1 mm or more and no methadone maintainance patients taking 30 mg of methadone or more a day will have apupillary constriction as great as 1 mm. We found that roughly one fourth of the addicts identified by all the usual criteria, including urines positive for morphine, had pupillary constrictions of greater than 1 mm indicating that they were minimally physically dependent, if they were physically dependent at all. The history could be used to predict those having minimal dependence. This study is consistent with other studies in which addict populations were tested with naloxone. Roughly one quarter of the addicts tested in these studies did not get precipitated withdrawal. Unfortunately these studies did not match drug use history with outcome of naloxone testing.

The accounts of addicts can give an internally coherent dynamic account of their addictive behaviors in which drug effects are consistent with current scientific evidence. In particular, I recall the history of a woman involved in an accident in which suicidal psychology on the part of this patient could be excluded by the circumstances of her accident. Without the accident it is not likely, given her psychology and social conditions, that she would have ever taken narcotics on any other than a medical basis and her general psychology and family history suggest that she would not have become a drug abuser. Her injuries were chronic and necessitated frequent narcotic administration. Her description of her gradual awareness that there could be pleasure from these drugs without reference to pain relief, and the fact that they could also have stress relieving effects, led her, after a period of years, to begin a pattern of addictive behaviors involving opioids in response to expectable but still severe life stress. Her account was consistent with all the data we have and defines the best case scenario for case reports.

The useless, sometimes misleading. end of the spectrum of clinical reporting: Daily clinical experience supported by the studies described above did not prepare me for the results of another study we carried out when addicts in my clinic were reporting high rates of use of diazepam both to enhance intoxication and for a variety of "therapeutic" purposes (Senay et al. 1977). These reports occurred before benzodiazepines could be tested for on a routine basis. I sought and obtained resources for special testing for benzodiazepines which I carried out, in blind fashion, on all urines for one month on all patients in my clinic. The results of the blind testing revealed that the addicts were actually taking propoxyphene, not diazepam. Griffiths carried out a study in which drug experienced addicts reported that they preferred benzodiazepines over barbiturates on the street, but under double blind conditions they consistently chose barbiturates rather than benzodiazepines (Griffiths et al., 1980).

Studies like these combined with clinical experience with "look alikes" in which drug users report drug effects of the drug they believe they are using rather than the effects of the drug they are actually using lead me to be quite cautious of reports of "street" preferences and actual use of "adjunctive" drugs.

The confounding effects of multiple drug use: In the course of studying the "T's and Blues" epidemic we went out on the street and contacted drug users not in treatment who alleged that they were using pentazocine. We purchased the pills they identified as "T's" from them and also paid them to give us a urine. The pills we purchased were most frequently indeed "T's." In many of these subjects we identified more than nine common substances of abuse not counting nicotine. It was clear that they were taking many drugs whose nature was unknown to them because the drugs they told us they were using were fewer in number than the number of drug classes we were detecting.

As our study of the "T's and Blues" users on the street indicated, multiple drug use has become the norm. Most admissions to drug treatment in recent years are using substantial amounts of one or more primary intoxicants and also are using substantial amounts of secondary drugs. With high doses of intoxicants such as cocaine base and the newer potent forms of marijuana it is probable that drug users, frequently, cannot register how much and what they are using with any degree of accuracy. Given the foregoing it is difficult to track the abuse liability of any single drug, new or old, when there are possibilities of drug interactions and severe cognitive and memory impairments.

The confounding effects of psychopathology: Another source of error in case reports is the difficulty in separating psychopathology from drug effects. Most intoxicants can produce symptoms and/or syndromes which can mimic almost any kind of psychopathology. In a given case it may be impossible to separate depression resulting from chronic drug use from naturally occuring depression. A classic example is in case reports of severe withdrawal in which a clinician biased against a given drug class forgets that stress of any kind usually worsens psychopathology and that withdrawal from any drug of dependence is a major stress. All the resulting symptoms are then attributed to the drug without due consideration of the pre-existing psychopathology and its possible contribution to variance.

The lack of precise terms and the lack of substance abuse training in medicine in general makes reporting problematic in manv instances: The lack of a generally agreed on terminology also presents difficulties. Diagnostic criteria for abuse and dependence change with each version of DSM III and it is likely that we will see more changes when DSM IV comes out in 1990. The clinician is then frequently without clear guidelines when making diagnoses. Many of the terms we use in the field of substance abuse are not defined. Intoxication, for example, has no scientific definition. It would appear that the intoxication from cocaine is different from intoxication from heroin which is different from intoxication from alcohol but we have no language to be precise about the differences. It is a lamentable fact but true that medical training is fifty years behind developments in the field of substance abuse. This means that most practitioners are untrained and inexperienced in the field. They are not in position to observe or to report accurately as a result.

The variance in populations: Individuals value drug effects generally with some consistency, but there is variation. Most users of pentazocine and tripelennamine confined their doses to two to three times the ordinary intoxicating dose because the margin between intoxicating doses and convulsions with this combination is very narrow. Most users of the combinations had experienced convulsions and wanted to avoid them and so limited their doses, but I had a few patients in my clinic who valued the convulsions and took doses they knew would induce them.

The responses of poly-drug abusers appear to be quite different from those not given to frequent use of multiple intoxicants, as is illustrated by the fact that normals prefer placebo to benzodiazepines but poly-drug abusers find these drugs pleasurable (DeWit et al., 1984). These two examples illustrate that there can be considerable variance attributable to persons which appear to have little to do with pharmacology.

COMMENT

In this review of case reports in Phase 4 we have seen an underlying spectrum of possibilities defined on one end by an accurate observer reporting to an accurate recorder effects which are consonant with the results of scientific study and which appear to have high reliability and validity; the other end of the spectrum consists of reports which are not consonant with science and appear to have no relation to pharmacology and are either grossly misleading or are simply valueless. This review also suggests that despite the many drawbacks of case reports in Phase 4 that they have functioned as the detection device for almost all abuse liability problems. The application of the "human testing" technology reviewed in this symposium promises to make less important the role of case reports and, hopefully, to make them of purely historical interest in the not too distant future.

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CHAPTER 12

United States Epidemiologic Data on Drug Use and Abuse: How are They Relevant to Testing Abuse Liability of Drugs?

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INTRODUCTION

Jaffe and Jaffe (this volume) have proposed that laboratory research on subjective drug effects has passed into adulthood after a tumultuous adolescence. By contrast, epidemiologic work on comparative testing for psychoactive drug self-administration and drug hazards is much less advanced, if we rely on a similar scale of progress.

In this paper we outline some directions of epidemiologic work that grow toward a capacity for comparative drug testing. However, major obstacles remain, and three will be stressed. First, the abuse liability concept may not serve well in the epidemiologic context where manifestations of drug-taking and drug hazards are heterogeneous, and where uncontrolled determinants are multiple. Second, in studies of medicine hazards, we often can rely on the hazardsoccuningatrandomwithrespecttoindications for medicine use or other antecedent conditions. As we shall see, this probably is not the case for many psychoactive medicines. In this context, the indications for medicine use (e.g., depressed mood) often are associated with occurrence of drug hazards (e.g., suicide by overdose). As a result, it sometimes will be necessary to exchange the usual observational strategies of epidemiology for random allocation designs in medical practice settings, if we hope to get good answers to questions about relative drug hazards.

A third major obstacle to progress concerns the nature and quality of the surveillance data. The epidemiologic data now available for comparative testing of controlled substances in the United States are gathered mainly by routine surveillance systems not oriented specifically to this task. The

resulting surveillance data sometimes can be put to good use, as we shall see, but not necessarily to good use in comparative drug testing.

UNPACKING ABUSE LIABILITY

Abuse liability and abuse potential are rich concepts densely packed with meaning. These concepts remain difficult, even if abuse liability is divided into liability for abuse and liability of abuse, an intuitively appealing approach proposed for behavioral pharmacology (Griffiths et al., 1986; Roache and Griffiths this volume).

As defined, the liability for abuse associated with a drug refers to drug-taking with a socially unacceptable purpose. Liability for abuse encompasses initial self-administration of a drug outside the scope of medical authority, or more than was prescribed; repeat self-administration; a single episode of emptying the medicine cabinet and ingesting all of its contents in order to commit suicide; and so on. To be sure, there may be a single theme underlying all of these behaviors: one latent trait or class may be the model that fits the data best. Nonetheless, until alternative models are tested, it seems plausible that the drug-taking behaviors encompassed by liability for abuse are quite heterogeneous, too heterogeneous for the goal of comparative drug testing in an epidemiologic context.

In contrast, a drug's liability of abuse has been defined in relation to the hazards of psychoactive drug use. The heterogeneity of drug hazards may be self-evident, but it may be helpful to show a set of illustrations that involve users of heroin, marijuana, and cocaine.

These illustrations are based on analyses of data from the National Institute of Mental Health Epidemiologic Catchment Area (ECA) Program. The ECA program was a five-site collaborative study in the United States, involving probability samples of area residents age 18 years and older in New Haven, Baltimore, St. Louis, Durham, and Los Angeles. In all, 20,862 subjects were interviewed for this study between 1980 and 1984, representing about 75 percent of the sampled respondents.

In the general ECA survey design, the Diagnostic Interview Schedule (DIS) was administered by trained lay interviewers at baseline and again atfollowup approximately one year later. About 80 percent of the baseline respondents participated at followup. Details of this study are published elsewhere (Eaton and Kessler 1985; Regier et al., 1988; Eaton et al., in press, a).

The DIS included a standardized battery of interview items to assess drug use by self-report, as well as self-reported consequences of drug use. Each of these interview items was written to correspond with a diagnostic criterion for drug abuse-dependence syndromes defined in the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) (APA 1980; Anthony and Helzer, in press, a). Responses to these items and to the items that concern other psychiatric syndromes and mental disorders were analyzed by computer, which yielded computer-based diagnoses (Robins et al., 1985).

In the ECA Program generally, no psychiatrists or clinical personnel examined the subjects or the individual data gathered by the DIS interviewers. However, the DIS was intended to make diagnoses comparable to those produced by a psychiatrist. Initial results on this count were promising, especially for DSM-III drug abuse-dependence and alcohol abuse-dependence categories (Robins et al., 1981). Community studies have been somewhat less promising (Anthony et al., 1985; Helzer et al., 1985; Shrout et al., 1987).

Table 1 shows the pattern of consequences of drug use reported by ECA respondents, in relation to level of drug involvement for a comparison of marijuana, cocaine, and heroin users. The DIS distinguishes daily users from those who used a drug on six or more occasions, but it does not yield drug-specific data on lower levels of use. For this reason, in most ECA publications and in this paper, a drug user generally is defined as one who has used a drug on six or more occasions. This eliminates so-called "purely experimental" users, with some unknown influence on relationships to drug hazards.

Among the ECA participants, there were 297 who identified themselves as having used heroin on a daily basis for 2 weeks or more, and there were 123 who reported heroin use on more than five occasions, but never daily for 2 weeks or more. Many of the daily drug users in the ECA samples were adult residents in correctional facilities and drug treatment programs, selected for study by probability sampling, not by self-selection or convenience sampling. Since the probability of selecting institutional residents greatly exceeded the probability of selecting residents of households, epidemiologic estimates for the total household and institutional population depend upon sample weighting procedures and adjustments for non-participation (Eaton and Kessler 1985; Regier et al., 1988). The weighting procedures can be used to give site-specific estimates as well as estimates based on pooled data. To aid the reader, we have not presented site-specific estimates in this paper. The site-specific estimates generally reflect the trends and tendencies shown in the pooled estimates given in table 1.

Table 1. Consequences of drug use reported by identified users of heroin, cocaine, and marijuana.

	HEROIN USERS	COCAINE USERS	MARIJUANA USERS
Number of users, by level:			
—Sustained daily users	297	300	1394
—Never daily users	123	749	1863
Percent of users			
Who felt dependent			
—Sustained daily users[1]	71.2 (6)	23.6 (4)	17.2 (*)
—Never daily users	8.9 (4)	2.2 (*)	1.3 (*)
Who had withdrawal sickness			
—Sustained daily users	68.2 (6)	18.2 (4)	2.9 (*)
—Never daily users	9.5 (4)	1.1 (*)	0.2 (*)
Who needed larger amounts			
—Sustained daily users	66.4 (6)	43.1 (5)	20.6 (1)
—Never daily users	11.9 (4)	8.2 (1)	3.4 (*)
Who failed to reduce use			
—Sustained daily users	40.5 (7)	14.4 (4)	8.4 (1)
—Never daily users	3.4 (2)	2.4 (*)	1.1 (*)
With social problems attributed to drug use			
—Sustained daily users	58.4 (7)	27.6 (4)	17.0 (1)
—Never daily users	13.8 (4)	3.8 (*)	3.6 (*)
With psychological problems attributed to drug use			
—Sustained daily users	43.2 (7)	25.3 (4)	20.6 (1)
—Never daily users	8.7 (4)	5.2 (1)	9.6 (*)
With other health problems attributed to drug use			
—Sustained daily users	24.2 (6)	10.1 (3)	4.6 (*)
—Never daily users	14.5 (4)	0.8 (*)	1.9 (*)

Note: Data from the NIMH Epidemiologic Catchment Area surveys in New Haven, Baltimore, St. Louis, Durham, and Los Angeles, 1980-84.

[1] These are estimates produced by pooling and weighting the sample to compensate for selection probabilities and non-response. Values for "never daily" users are based on four sites; the New Haven survey identified daily users only. Values in parentheses are standard error estimates (percent), * = <0.01.

As table 1 shows, after pooling the data from all five ECA sites and after taking probability of subject selection into account, an estimated 71.2 percent of the daily heroin users reported having felt dependent on heroin. By comparison, an estimated 8.9 percent of the never daily users reported having had feelings of dependence on heroin. This difference in percentages from about 9 to 71 percent is consistent with presumed toxicity of nondaily heroin use versus daily heroin use.

Before proceeding, it is important to draw attention to the nature of the statistical measure being reported here. This measure is an estimated lifetime prevalence proportion based on ECA data. For example, 71 percent of daily heroin users reported having felt dependent on heroin. This was derived by estimating the number of identified daily heroin users who felt dependent, divided by the estimated total number of daily heroin users at the time of the survey. Based on cross-sectional survey data, the lifetime prevalence values represent crude approximations of more standard and informative epidemiologic measures such as the cumulative incidence and incidence density, defined elsewhere (e.g., Rothman 1986). Nevertheless, in the absence of prospective studies the lifetime prevalence proportions given here are now the best available estimates for cumulative incidence proportions.

Summarized below, there also were differences in percent reporting consequences across two levels of heroin involvement uniformly held up for cocaine use and marijuana use. Further, with one exception, subjects reporting heroin use were more likely to report drug-related adversity than the cocaine users. In general, subjects reporting cocaine use were more likely to report adversities than marijuana users.

Among the 300 ECA subjects who identified themselves as having used cocaine on a daily basis for 2 weeks or more, an estimated 23.6 percent reported having felt dependent on cocaine; the corresponding estimate for 749 “never daily” cocaine users was 2.2 percent. Among the 1394 ECA subjects who identified themselves as having used marijuana on a daily basis for two weeks or more, an estimated 17.2 percent reported having felt dependent on marijuana, while an estimated 1.3 percent of the 1863 “never daily” marijuana users reported having felt dependent.

The findings on withdrawal symptoms reported by heroin and cocaine users were virtually identical to those for self-reported feelings of dependence, but this was not the case for the marijuana users. Among the daily marijuana users, only 2.9 percent reported having felt sick due to

stopping or cutting down on marijuana use. The corresponding estimate for the "never daily" marijuana users was 0.2 percent.

The DIS assessed drug tolerance by means of the following interview question, "Did you find that you needed larger amounts of these drugs to get an effect—or that you could no longer get. high on the amount you used to use?" An estimated two-thirds of the daily heroin users, 43 percent of the daily cocaine users, and 21 percent of the daily marijuana users reported this experience. The never daily users were about one-sixth as likely to describe themselves as having needed larger amounts.

Another DIS interview question on drug dependence sought reports about failed attempts to stop or cut down on drug use. It is noteworthy that only 40 percent of the daily heroin users reported this experience with heroin, as compared to 14.4 percent of the daily cocaine users and 8.4 percent of the daily marijuana users. Failed attempts to cut back were reported by 3.4 percent of the never daily heroin users, 2.4 percent of the never daily cocaine users, and 1.1 percent of the never daily marijuana users.

To address socially maladaptive behavior that might follow from drug use, the DIS posed questions about drug-related problems with the police, on the job, or involving family and friends. An estimated 58.4 percent of daily heroin users reported these problems, as did one-half as many daily cocaine users (27.6 percent), and roughly one-third as many daily marijuana users (17 percent). Whereas three to four percent of the never daily cocaine users and marijuana users reported social problems, an estimated 13.8 percent of never daily heroin users reported social difficulties related to heroin use.

In response to DIS questions on psychological or emotional troubles due to drug use, daily heroin users and daily cocaine users were five times more likely to report these problems as compared to corresponding never daily users. The difference across levels of marijuana involvement was not so steep: an estimated 20.6 percent of the daily marijuana users reported psychological problems due to marijuana use as compared to an estimated 9.6 percent of the never daily marijuana users.

Other health problems due to drug use (e.g., a persistent cough, overdose, convulsions) were reported by 24.2 percent of the daily heroin users and 14.5 percent of the never daily heroin users. These health problems were reported by 10 percent of the daily cocaine users, but virtually none (0.8 percent) of the never daily users. Fewer than five percent of the daily marijuana users and only 1.9 percent of the never daily marijuana users reported other health problems due to marijuana use.

Table 2 extends the illustration of heterogeneity among drug hazards to other classes of controlled substances and to other potential hazards and consequences of drug use, including the proportion who had become daily users and the proportion who had become cases of DIS/DSM-III drug abuse-dependence syndromes. In studying this profile it may be useful to take heroin as a reference for comparison. Unfortunately, the DIS did not capture, in usable form, any distinctions between drug compounds within the groups shown here. This is a general weakness in current drug abuse interview survey methods, one that limits a capacity for comparative drug testing.

Based on pooled and weighted estimates from the ECA household and institutional samples, an estimated 40 percent of heroin users reported having used heroin for 2 weeks or longer. By comparison, an estimated 14 percent of cocaine users and 33 percent of marijuana users identified themselves as having a history of sustained daily use. Corresponding estimates for other psychostimulants besides cocaine, for the anxiolytics assigned to federal schedules, for other sedative-hypnotics, and for hallucinogens were 25 percent, 18 percent, 18 percent, and 10 percent, respectively, as shown in table 2. Thus, despite the presumed greater mortality of heroin users, these data suggest that a larger proportion of heroin users had become daily users as compared to users of the other drugs. However, it is notable that the observed rank-ordering of heroin, cocaine, and marijuana did not follow the ordering from laboratory studies of drug self-administration described by others. This draws attention to conditions such as relative availability of marijuana as compared to other drugs, which clearly can affect repeated drug self- administration outside the laboratory, perhaps more than any inherent reinforcing properties of these drugs.

An estimated 44 percent of the identified heroin users qualified as current or former cases of DIS/DSM-III opioid abuse and/or opioid dependence. By comparison, about one-fifth of the identified marijuana users qualified as current or former cases of DIS/DSM-III cannabis abuse and/or cannabis dependence. Similar estimates were obtained for users of psychostimulants besides cocaine, for scheduled anxiolytics, and for other sedative- hypnotic drugs.

One item of note is the low value for the DIS diagnosis of cocaine abuse (3 percent). This seems to be due in part to an idiosyncracy in the DSM-III and also in the DIS computer algorithm, subsequently revised in DSM-IIIR but not yet implemented in the DIS. Another factor contributing to the low values observed for both cocaine and the hallucinogens is that DSM-III defined no dependence category for users of these drugs.

Table 2. Characteristics of identified drug users, by drug group.

Drug Group (Number of users)	Estimated proportion with a history of sustained daily use	Estimated proportion with DIS abuse-dependence involving this drug	Estimated proportion of current users among those who had ever used	Estimated proportion of recent users still using the drug one year later
Users of heroin (359)	40 %	44 %	11 %	18 %
Users of marijuana (2977)	33	20	51	43
Psychostimulant Drugs				
Users of cocaine (975)	14	3	33	23
Users of other psychostimulants (1055)	25	20	18	11
Anxiolytics-Sedatives-Hypnotic Drugs				
Users of scheduled anxiolytics (656)	18	17	17	9
Users of other CNS depressants (740)	18	23	16	12
Users of hallucinogens (647)	10	8	9	5

Note: Data from NIMH Epidemiologic Catchment Area surveys in Baltimore., St. Louis, Durham, & Los Angeles, 1980-84
All estimates, except those in the last column, were produced by applying sample weighting procedures and by compensating for survey non-response at the local level. Approximate standard errors ranged from one percent (marijuana estimates) to five percent (heroin estimates), but typically were close to two percent. The number of drug users identified in the four ECA samples is shown within parentheses associated with each drug group. The New Haven site is not represented in this table, and the St. Louis site is not represented in the estimates concerning current and recent users -- the necessary interview items were not included in the surveys there.

Up to this point, these ECA estimates have dealt with the lifetime history of specific drug hazards, such as feeling dependent, having social problems, becoming a daily user, or becoming a case of drug abuse or dependence. Table 2 also shows estimates for the proportion of current drug users, who were current users with current use defined as use within the one month prior to the survey. These estimates indicate that current marijuana use was characteristic of about one-half of those who identified themselves as having used marijuana on more than five occasions. About one-third of the identified cocaine users were current users. Estimated values for the other drug groups ranged from 9 percent (hallucinogens) to 18 percent (psychostimulants other than cocaine).

The last column of table 2 shows data from ECA followup interviews conducted one year after the initial survey. The estimates are based on the subjects who identified themselves as having used specific drugs within one year of the initial survey, and who were interviewed atfollowup. Each drug-specific estimate in the column is the unweighted proportion of these subjects who reported they still were using at the time of followup. According to the DIS, and subject to limitations of the followup method, marijuana users identified in the initial interview were most likely to be using one year later: 43 percent of them reported using marijuana within two weeks prior to the followup interview. About one-half as many cocaine users (23 percent) still were using cocaine one year after the initial interview. The corresponding estimate for heroin users was 18 percent. Estimates for the other drug groups ranged from 5 percent (hallucinogens) to 12 percent (sedative-hypnotics other than scheduled anxiolytics).

The foregoing data serve to illustrate the heterogeneity of consequences and hazards of drug use in the epidemiologic context, and by extension the multiple determinants of these drug hazards, including conditions such as drug availability. Nevertheless, there is something inherently dissatisfying when analysis of drug consequences is limited to the domain of drug-related behavior and to self-reported and self-attributed consequences of drug use. One reason for dissatisfaction is uncertainty about drug users' capacity to know and to report the consequences of drug use (Anthony and Petronis, in press, b, c). Another problem is that both drug use and these drug consequences have been measured with self-report interview techniques. To some extent, this similarity of methods artificially elevates the degree of association between drug use and suspected consequences.

For this reason, we have extended the range of consequences to specific categories of psychiatric disorders, though there still is a problem of

shared methods co-variation. The psychiatric disorders were assessed by the DIS, as was the syndrome of drug abuse-dependence. However, neither the interviewers nor the respondents were aware that these associations would be tested.

Because we sampled residents of prisons, mental hospitals, and alcohol or drug treatment programs, we have developed separate estimates for the various sample segments, including the household segment. This allows us to depict a frequently neglected potential bias of clinical and convenience samples of drug abusers. To control for age and sex as potential confounding variables, this analysis has been restricted to males 18-44 years old.

Table 3 gives the number of 18-44 year old male participants sampled from correctional facilities; from psychiatric, alcohol, and other drug treatment facilities; and from households. Table 3 also shows that an estimated 58 percent of the correctional inmates, 38 percent of the treatment facility residents, and 12.3 percent of the household residents were current or former cases of DIS/DSM-III abuse and/or dependence involving controlled substances. (Alcohol abuse-dependence was not counted in these estimates.)

The estimated lifetime prevalence of DIS/DSM-III antisocial personality disorder (ASP) among correctional inmates with a history of drug abuse-dependence was 55 percent. Corresponding estimates for cases of drug abuse-dependence found in treatment facilities and in the household population were 58 percent and 37 percent. By comparison, the ASP lifetime prevalence estimate was only 10 percent for household residents not qualifying as current or former cases of DIS/DSM-III drug abuse-dependence. As indexed by the ratio of lifetime prevalence estimates for persons with and without a history of drug abuse-dependence, there was an association between drug abuse-dependence and ASP, consistent with prior research on males summarized elsewhere (e.g.,Robins 1978; Kellam et al., 1983; Anthony 1985; Robins and Przybeck 1985). These data on ASP and drug abuse-dependence illustrate how studies of suspected causal associations based solely on drug abuse-dependence cases located in correctional facilities or in clinical samples might yield biased estimates, as compared with those based on total population samples. The ASP lifetime prevalence ratio of 0.38 to 0.10 based on the total sample was 3.8. Corresponding ratios based on correctional inmates (0.55:0.10) and cases in treatment (0.58:0.10) were larger, 5.5 and 5.8, respectively.

Whether these ratios of lifetime prevalence proportions accurately reflect a causal association between ASP and drug abuse-dependence cannot be

Table 3. Estimated lifetime prevalence proportion for selected DIS/DSM-III mental disorder categories among males 18-44 years of age, by place of residence, and in relation to DIS/DSM-III abuse-dependence syndromes involving controlled psychoactive drugs.

	PLACE OF RESIDENCE:			
	Correctional Facilities	Psychiatric, drug, and alcohol Treatment Facilities	Households	All Sample Segments
Number of subjects sampled:	550	131	3755	4436
Estimated lifetime prevalence of pychoactive drug abuse-dependence	58%	38%	12.3%	12.5%
Estimated lifetime prevalence (%) of Antisocial personality disorder				
- Among cases of drug abuse-dependence	55	58	37	38
- Among those with no abuse-dependence	*	*	10	10
Estimated lifetime prevalence (%) of Major depression				
- Among cases of drug abuse-dependence	19	32	14	14
- Among those with no abuse-dependence	*	*	4	4
Estimated lifetime prevalence (%) of Panic disorder				
- Among cases of drug abuse-dependence	4.3	7.4	3.1	3.2
- Among those with no abuse-dependence	*	*	0.9	0.9

Note: Data from the NIMH Epidemiologic Catchment Area surveys in New Haven, Baltimore, St. Louis, Durham, and Los Angeles, 1980-84.

All estimates weighted and adjusted for survey non-response at the local level.

* indicates "not estimated."

METHODOLOGICCOMMENT: It is notable that the prevalence estimates based on the household segment of the survey sample were not too distant from those based on all sample segments (shown in the last column of the table). This is a reflection of the relatively small proportion of younger adult males living in institutions and group quarters, as compared to the much larger proportion living in households.

answered here. Analyses of lifetime prevalence data typically cannot distinguish temporal antecedents from temporal successors. There is an association here, with history of ASP being more common among drug abuse-dependence cases, but the analysis cannot determine which disorder came first. Moreover, the problem cannot be solved by asking for age of onset of each disorder, unless the disorder has an abrupt onset (Robins and Przybeck 1985; Anthony and Helzer, in press, a). For disorders such as major depression, antisocial personality disorder, and drug abuse-dependence syndromes, the onset typically is insidious, not abrupt. Cases may be able to specify events such as first drug-taking or first suicide attempt, but these events do not necessarily signal onset of the disorder.

The other estimates shown in table 3 point toward possible associations of drug abuse-dependence with major depression and panic disorder, for example, as indexed by taking the ratio of lifetime prevalence values. The comparison of ratios across sample segments, taking the household estimate for persons without drug abuse-dependence as an expected value, again shows how clinical samples might lead to upwardly biased estimates of association between drug abuse-dependence and psychiatric conditions.

Epidemiologic evidence on possible associations of drug abuse-dependence syndromes with DIS/DSM-III major depression and panic disorder complements and extends prior clinical case reports and studies of clinical samples (Anthony and Petronis, in press, c). On one hand, in considering the ECA data, there is some basis for concern because the DIS diagnoses were not made by experienced clinicians. On the other hand, use of the DIS method precluded any influence of diagnostic suspicion bias, workup bias, or related biases that are difficult to control when clinicians must assess psychiatric disorders among drug users (Senay, this volume).

Table 4 provides an analysis of psychiatric disorder status in relation to ordered levels of involvement with marijuana, heroin, and cocaine, based on males and females 18-44 years old in the ECA sample. Users who qualified for the DIS abuse-dependence diagnosis were considered to be most involved. In reverse order of involvement, those with sustained daily use but no diagnosis were next, followed by the other two groups of users. The trends observed for both sexes were generally comparable to those observed for males and females separately.

With all the strengths and limitations of these cross-sectional and lifetime prevalence data, the results generally point toward predicted trends

Table 4. Suspected hazards of drug use among 18-44 year olds, by level of drug involvement: DIS/DSM-III Major Depression, DIS/DSM-III Panic Disorder, and use of emergency room services for problems with alcohol, other drugs, or mental health (ADM).

A. Number of 18-44 year old subjects in each group[1]

Level of Drug Involvement	Cocaine	Mariiuana	Heroin
Used 0-5 times	8665	6483	9233
Used >5 times, never daily	713	1597	89
Used daily: two weeks or more	209	779	16
Qualified for DSM drug disorder	98	837	347

B. Percent found to be current or former Major Depression cases[2]

Level of Drug Involvement	Cocaine	Marijuana	Heroin
Used 0-5 times	7.6 (*)	6.7 (*)	7.8 (*)
Used >5 times, never daily	11.0 (2)	8.0 (*)	6.7 (4)
Used daily: two weeks or more	14.6 (4)	13.2 (2)	17.4 (16)
Qualified for drug diagnosis	25.8 (10)	15.3 (2)	23.0 (5)

C. Percent found to be current or former Panic Disorder cases[2]

Level of Drug Involvement	Cocaine	Marijuana	Heroin
Used 0-5 times	1.7 (*)	1.7 (*)	1.7 (*)
Used >5 times, never daily	2.4 (*)	1.7 (*)	3.9 (3)
Used daily: two weeks or more	2.3 (2)	1.8 (*)	16.9 (16)
Qualified for drug diagnosis	15.3 (8)	3.2 (*)	9.2 (4)

D. Percent reporting visit to emergency room for ADM problem[2]

Level of Drug Involvement	Cocaine	Marijuana	Heroin
Used 0-5 times	3.4 (*)	3.2 (*)	3.7 (*)
Used >5 times, never daily	5.5 (1)	2.7 (*)	13.1(6)
Used daily: two weeks or more	2.3 (5)	8.0 (2)	0.1 (2)
Qualified for drug diagnosis	25.2 (11)	9.1 (2)	12.9 (5)

Note: Data from NIMH Epidemiologic Catchment Area surveys in New Haven, Baltimore, St. Louis, Durham, and Los Angeles, 1980-84.

[1] Some analyses based on slightly smaller numbers, due to missing values on some variables.

[2] Approximate standard errors are (percent) within parentheses (*= <1.0)

involving cocaine and, to a somewhat lesser extent, marijuana and heroin as well. For example, an estimated 7.6 percent of the 18-44 year olds with fewer than six occasions of cocaine use qualified for the DIS/DSM-III diagnosis of major depression. At the other extreme of involvement with cocaine, 25.8 percent of the DIS/DSM-III cocaine abuse cases qualified for the major depression diagnosis. Estimated lifetime prevalence values for other levels of cocaine use were intermediate. Corresponding estimates for levels of marijuana involvement were lower than those for cocaine, but a roughly similar trendemerged. Arelatedtrend, with some irregularity, also was present in estimates for levels of heroin involvement.

Table 4 shows a somewhat different pattern of association in relation to DIS/DSM-III panic disorder. It was the DIS/DSM-III cocaine abuse cases who were most likely to qualify for the panic disorder diagnosis (15.3 percent), but the lifetime prevalence of panic disorder was under 3 percent for the other levels of cocaine involvement. Low panic disorder prevalence values also were characteristic of the lower levels of marijuana involvement, while 3.2 percent of the DIS/DSM-III cannabis abuse-dependence cases qualified for the panic disorder diagnosis. The panic disorder prevalence values also tended to increase in relation to heroin involvement. (The value for daily heroin users who did not qualify for opioid abuse or dependence may be understood in relation to the small number of daily users in this group; the standard error was large.)

Data presented in table 4 also describe an aspect of health services utilization by level of involvement with marijuana, cocaine, and heroin. As table 4 shows, some 12 to 25 percent of the cocaine and heroin abuse or dependence cases had received emergency room care for alcohol, drug, emotional, or mental problems, as compared to 9.1 percent of the marijuana cases. For marijuana and cocaine, there was a trend for increasing likelihood of having received such care with increasing level of drug involvement. For heroin, this trend was not regular, due to a low value for daily heroin users who did not qualify for the DIS/DSM-III opioid abuse-dependence.

The purpose of this set of illustrations was to clarify the heterogeneity of the hazards encompassed by liability of abuse in the context of epidemiology. The illustrations also clarify how epidemiologic evidence can become more important in comparative drug testing, provided the epidemiologic strategies and methods are strengthened. For example, the DIS assessment of drug use was limited. In future work, the assessment of specific marketed drug products can be expanded to include use of color pill charts pioneered by Balter and his colleagues in research on

psychotherapeutic medicines (Parry et al., 1971), possibly to include testing of biological samples for corroboration of reported use. These methods have been used in some drug abuse surveys, but with no attempt to capture detailed information about specific drug compounds beyond lifetime history of use or recent use.

Another important effort will be to clarify the temporal sequence between drug use and occurrence of psychiatric disorders. This is an issue that is left unresolved in analysis of lifetime data of the type gathered in the ECA interviews.

To conclude this section of the paper, we reiterate our suggestion that hazards of drug use, drug-seeking, and drug-taking likely are too heterogeneous to be grouped under the proposed rubrics of liability for abuse and liability of abuse. It may be possible to test the two-group model empirically, using latent variable analyses of a type already used to study psychiatric syndromes (Blazer et al., 1988; Eaton et al., in press, b). In the interim, it may be most useful to unpack the abstract concepts and discard the terminological baggage once they have been emptied of meaning. The terms "liability" and "potential" conjure up an attribution of influence to the drug, without balancing the relative influences of drug, host, and environment. Even if the two-group model were to fit the data as well or better than any other, this attribution problem provides a basis for changing the terminology.

CONFOUNDING

In table 5, we introduce the problem of confounding with an example of a within-drug comparison concerning the relative hazard associated with three routes of administering cocaine. In data from the 1985 Drug Abuse Warning Network (DAWN), about 13,500 drug episodes involving cocaine were reported by emergency rooms in the network. Of these, 39 percent had a mention of cocaine taken by injection. The next highest proportion corresponded to the inhalation route (U.S. 1986a).

The large value associated with injection was expected, based on a credible and well-founded suspicion that cocaine use by injection is more hazardous than other routes of administration. Exploring this hypothesis more thoroughly required some information about the population of cocaine users not admitted for emergency room care. There was no need for an absolute number, but it was necessary to have some idea of the proportion of users who inject on any given day. Preferably this estimate would come from the cities where DAWN facilities are located.

Table 5. Is injecting cocaine associated with increased risk of becoming an emergency casualty?

	Drug Abuse[2] Warning Network Emergency Rooms. 1985	National [3,4] Household Drug Survey 1985	National Survey of Drug Treatment Programs 1985.
Number and percent distribution of cocaine users by method of cocaine administration:			
Approximate no. of users:	13,501	1,000	13,000
Percent with:			
Cocaine use by injection	39%	8%	20%
Cocaine use by inhalation*	35	95	52
Cocaine use by smoking	10	21	26
Unknown or other methods	16	12	0

Note: Data from the Drug Abuse Warning Network, the National Household Survey on Drug Abuse, and a national survey of clients admitted to drug treatment programs, United States, 1985.

[1] Inhalation by nose or mouth, except by smoking.

[2] The Drug Abuse Warning Network is an event-based reporting system. The approximate number of users is based on the number of drug mentions.

[3] The household survey allowed multiple responses to the interview question on which routes of administration had been used. In contrast, the DAWN is concerned with the method of administration proximal to admission to the emergency room, and the survey of clients in drug treatment programs is concerned with methods of administration at the time of admission to the program.

[4] The method described by Finney (1980) was used to estimate the degree to which cocaine injectors are at increased risk of becoming a DAWN emergency room casualty. The text mentions risk ratio estimates derived by the following calculations:

With expected value from survey of household residents:

(13501*0.39*0.92)/(13501*0.61*0.08) = 7.3.

With expected value from survey of clients in treatment:

(13501*0.39*0.80)/(13501*0.61*0.20) = 2.6.

The closest available estimate for cocaine users as a group was based on aquestion in the 1985 national household drug survey which askedcocaine users if they ever had injected cocaine. Eight percent of users said they had (U.S. 1987a). This clearly is an underestimate relative to the actual frequency of cocaine injection among persons using cocaine on any given day, but it suggested a fairly strong degree of association between injecting cocaine and being admitted to an emergency room. This can be appreciated by thinking of the 8 percent value from the national household survey as an expected value against which to compare the 39 percent value from DAWN. Using Finney's method (Finney 1980), the risk of becoming an emergency room casualty among those who inject cocaine was an estimated seven times greater than the risk among non-injecting users (table 5).

There are several defects in this estimate. One defect that could be looked into is the possibility that the 8 percent expected value was inaccurately low. To check this possibility, we obtained data on 13,000 clients admitted to drug abuse treatment facilities in 1985, who had cocaine as the primary drug of abuse. In this group, 20 percent reported that they were cocaine injectors at the time of admission (U.S. 1987a). Using this estimate for the expected value and applying Finney's method, we estimated that the risk of becoming an emergency room casualty among cocaine users who inject was 2.6 times greater than the corresponding risk among non-injecting cocaine users (table 5).

This result may mean that injecting cocaine accounts for the increased risk. Nonetheless, despite plausibility of the inference, alternative explanations are possible. The main obstacle to inference is absence of control over confounding variables, such as concurrent heroin use. Heroin users are more likely to inject cocaine, and in addition heroin use seems to be associated with increased risk of being admitted to the emergency room (table 4).

We also have noted that an increasing proportion of DAWN reports mention cocaine smoking. This increase may be an indication that smoking crack cocaine is an especially hazardous drug use pattern, or it may be that the increase seen in DAWN data simply reflects the increased frequency of crackcocaine use in the general population. This open question deserves futher study.

Table 6 illustrates the confounding problem, using DAWN data on the benzodiazepines, with an adjustment based on market share estimated for each drug. Here, the number of DAWN emergency room reports

Table 6. Indices of the population's experience with specific benzodiazepine drugs in 1985.

	RX[1] Market Share (Millions)	No. of DAWN Emergency Room (ER) Episodes	ER:RX[2] Ratio	No. of DAWN Deaths	Death:RX[3] Ratio
Diazepam	23	7653	333	317	13.8
Alprazolam	11	3403	309	32	2.9
Lorazepam	10	1450	145	<10	*
Flurazepam	8	1517	190	40	5.0
Triazolam	7	1390	199	26	3.7
Chlorazepate	7	893	128	<10	*
Chlordiazepoxide	6	1360	227	43	7.2
Temazepam	5	844	169	13	2.6
Oxazepam	2	211	106	<10	*
Prazepam	2	274	137	<10	*

Note: Data from reports compiled for the Drug Abuse Warning Network, United States, 1985.

[1] The prescription market share (RX) refers to millions of prescriptions in a period of time roughly corresponding to the 1985 period of DAWN reports.

[2] The ER:RX Ratio is the number of DAWN emergency room episodes per million prescriptions.

[3] The Death:RX Ratio is the number of DAWN deaths reported by medical examiners per million prescriptions. (* indicates that the ratio was not estimated due to the small number of reported deaths.)

mentioning each of 10 benzodiazepines in 1985 and the corresponding number of Medical Examiner events (deaths) were related to the number of prescriptions for these drugs issued during a roughly comparable period of time. Estimates for the number of prescriptions were based on market research summarized in a government report on DAWN (U.S. 1988b).

In table 6, before and after the adjustment for market share, diazepam and chlordiazepoxide were near the top of the distributions. Temazepam was near the bottom. Triazolam was mid- range. However, drug comparisons based on relative frequency of DAWN emergency room episodes were

different from those based on DAWN death data. Moreover, this analysis also was subject to the problem of potential confounding or uneven distribution of factors that influence probability of harm. For example, users of diazepam may be more likely to be long- term users, as compared to the other drugs shown. Further, there may be confounding in the selection of patients for diazepam as compared to the other drugs. For example, the diazepam users seen in DAWN facilities may more often be methadone program clients or heavy drinkers of alcoholic beverages. Finally, it also is worth noting that the number of prescriptions written does not reflect the contribution of the street drug marketplace to casualties involving these drugs. The number of illicitly supplied diazepam users may be quite high, relative to the other drugs shown.

There is a tendency to interpret data of this type in hazard terms. For example, one might read these data and conclude that taking diazepam was most hazardous. Especially because of uncontrolled confounding, this conclusion cannot be drawn on the basis of these data.

The issue of confounding in comparative drug testing may be understood more clearly by thinking about which drugs are more hazardous to take in relation to suicide. As shown in table 7, the 1986 DAWN report indicated 152 suicide deaths involving amitriptyline, an antidepressant, as compared to 97 for diazepam and 18 for alprazolam (U.S. 1987b). We may wish to consider these raw values or to divide by the number of prescriptions. Either way the ranking could lead to the conclusion that diazepam causes more suicide than alprazolam and that amitriptyline causes more suicide than diazepam. (Though we did not have an estimate for amitriptyline's market share, it certainly was lower than that of diazepam. Hence, both the number of amitriptyline-related suicides and the ratio of deaths to market share exceed corresponding values for diazepam.)

On the basis of the available data, any conclusion that amitriptyline use made a greater contribution to suicide deaths would be no more justified than the conclusion that alprazolam actually has prevented more suicides than either diazepam or amitriptyline. (This might be suspected because the alprazolam values are lowest.) There is an unaddressable problem of confounding by indication in these DAWN data. It is quite plausible that diazepam and alprazolam are less likely to appear in relation to suicides simply because amitriptyline users are more likely to have a major affective disorder putting them at greater risk for suicide, The indications for amitriptyline use, as compared to those for diazepam and alprazolam, make it difficult to compare the hazards associated with each drug.

Table 7. Comparative analysis of suicide deaths and involvement of amitriptyline, diazepam, and alprazolam.

	Amitriptyline	Diazepam	Alprazolam
Number of death reports that mention the drug:	263	317	32
Percent of all such deaths judged to be drug-induced:	81	79	88
Number of the reports on suicide deaths that mention the drug:	152	97	18
Millions of prescriptions:	<23	23	11
Number of suicide deaths per million RX:	>4.2	4.2	1.6

Note: Data compiled for the Drug Abuse Warning Network based on reports from medical examiners offices, 1986.
Because the market share for amitriptyline is substantially smaller than the share for diazepam, we infer that the number of suicide deaths per million prescriptions is larger for amitriptyline.

In conclusion, the only way to interpret data of this type meaningfully is to make generally unrealistic assumptions that all confounding factors are distributed evenly across drug groups. In some instances it is possible to eliminate certain assumptions, for example, by using random allocation designs in post-marketing research. Alternately, it sometimes is possible to find special settings where some or all of the confounding factors have demonstrably even distributions, or nearly so. This was what Bergman and Griffiths were able to do in their work on relative abuse of diazepam and oxazepam in Sweden (Bergman and Griffiths 1986). Unfortunately, it often has been necessary to go outside the United States to find suitable settings for comparisons of this type. Finally, when ancillary data can be found for each important confounding variable, it sometimes is possible to use statistical models that hold the confounding variables constant. This is a strategy found to be generally useful in drug epidemiology that we also have taken in our own work on suspected causal associations between cocaine use and psychiatric disturbances, described elsewhere (Anthony et al., 1989; Anthony and Petronis in press, c).

THE NATURE AND QUALITY OF DATA

In the United States, the epidemiologic data available for comparative drug testing typically have been gathered for some other purpose. For example, the Epidemiologic Catchment Area surveys were designed as research on the occurrence of mental disorders in the population. There was no explicitly stated, advance plan to use these data for comparative drug testing. This accounts for some weaknesses of the ECA data when we have applied them to problems related to comparative drug testing.

Similarly, the currently available data from drug abuse surveillance systems like DAWN and the System to Retrieve Information from Drug Evidence (STRIDE) are gathered primarily to describe current drug abuse conditions and to monitor trends over time. By definition, these systems were designed for surveillance, which in epidemiology means an on-going review of a population's experience in sickness and health, generally with methods that are notable by their practicality, uniformity, and rapidity, not necessarily distinguished by accuracy or completeness (Last 1983). For this reason, it may be unreasonable to expect that these surveillance systems can provide information of a nature and quality suitable for comparative drug testing. As mentioned above and discussed in more detail elsewhere (Ungerleider et al., 1980: Anthony and Trinkoff 1986), there are important, unresolved questions about the capacity of surveillance systems like DAWN to provide accurate information about specific drug products. These questionsrelatenot only to the accuracy and completeness

of drug identification, but also to issues such as the responsivity of DAWN to pending drug control decisions or to media coverage of the street drug scene.

In thecontext of comparative drug testing through analysis of surveillance data, one problem that deserves greater attention stems from amultiplicity of possible comparisons. Due to a lack of broadly accepted guidelines or principles, it is possible for an interested party to dredge through masses of surveillance data, picking and choosing from among many possible drug comparisons and from among many possible statistical indices for comparison. When reading reports on the final comparisons, it is not always clear that the investigator approached the analysis with specific statistical indices or drug comparisons planned in advance. The element of opportunism, which increases the likelihood of spurious findings, is uncontrolled. Our discussion of table 6 illustrates this point.

CONCLUDING REMARKS

The subtitle for this paper asks, "How are epidemiologic data relevant to testing abuse liability of drugs?" Others have said or implied that what happens once a drug is released for use outside the laboratory should be the gold standard against which all abuse liability predictors are tested. As sketched out here, in principle, this is right, but it may be easier said than done.

Due to the myriad features and determinants of psychoactive drug-taking and drug hazards in the population, comparative testing of drugs for abuse liability by epidemiologic methods calls for refining concepts like liability for abuse and liability of abuse. These concepts now seem to attribute too much influence to the drug itself, too little to environment and host conditions under which suspected hazards are observed. In addition, due to the likely presence of confounding by indications for use, and possible confounding by other factors, it always will be difficult to produce unequivocal drug comparisons using observational epidemiologic strategies that do not contend with these possibilities for error in comparative drug testing.

Considering the nature and quality of epidemiologic data now available, we face a challenge if we are to use these data in comparative drug testing. The challenge is to state the principles that must be followed and the standards that must be met. At a minimum, it would seem that our standards should require concurrent analyses involving a pre-specified array of drug products and statistical measures of outcome. Tests of

assumptions about confounding by indication and other conditions related to drug use should become standard practice, as should tests of assumptions about quality of data being analyzed. Without these principles and standards for use of epidemiologic data, the elements of opportunism and selective attention are uncontrolled. Especially in exploration of surveillance data, it is too easy to pick out the drugs, outcome measures, and analytic techniques that serve one interest, one time. Without tests or critical review of assumptions, the epidemiologic work is incomplete.

In view of difficulties with present epidemiologic data now available in the United States, serious thought must be given to improving their quality. If we are to use DAWN and other routine reporting systems for more than surveillance, then some re-design will be needed to assure that these data meet minimal standards for the additional tasks, such as comparative drug testing. It is almost certain that the re-designing will require a major investment of time and effort by experienced pharmacologists and epidemiologists willing to be held accountable for the resulting products. At present, no one is making this investment. Perhaps this is a task-area that should be sponsored and given priority by the Committee on Problems of Drug Dependence.

When marketed psychoactive drugs are of interest, the problems of confounding by indication, and quality of data, may be best solved in the United States by shifting to the arena of large-scale medical practices and health plans. in some of these settings there is a capacity for careful observational studies and a willingness to have patients assigned to treatment conditions in order to account for indications and other potentially confounding conditions. This approach is an especially ambitious one that also requires a major investment by pharmacologists and epidemiologists, not to mention practicing clinicians in charge of patient care. Nevertheless, ambitious work of this type will be essential if the drug epidemiologist's contribution to comparative testing of psychoactive drugs is to live up to the high standards now set in laboratory research on this issue.

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CHAPTER 13

Current Approaches to Measurement of Drug Use and Abuse in Sweden

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David Lee, M.D.

INTRODUCTION

The use and abuse of barbiturates, organic bromides and amphetamines was described in Sweden in the 1930s. The development of the abuse in Sweden leading to the current restrictions in the prescribing of narcotic drugs introduced in 1962 has previously been reviewed (Goldberg 1968a; 1968b). These regulatory measures drastically reduced the number of prescriptions for narcotics, and several of these drugs, such as amphetamines, opiates and barbiturates, have been withdrawn from the market. Table 1 lists currently available drugs legally classified as narcotics (which includes some psychotropic drugs) in Sweden. The nine drugs on Schedule II and III are available in 13 trade names, all for parenteral use and four' also available in oral dosage forms. The 19 drugs on Schedules IV and V are available in 30 trade names, in oral dosage forms, and two[2] only for parenteral use. There has been a considerable reduction in the number of drugs and trade names since the late 1960s.

In agreement with the reported situation in the United States, the exaggerated fear of morphine abuse has also prevented cancer patients from receiving adequate pain treatment in Sweden (Marks and Sachar 1973; Agenäs et al., 1982). However, since the 1970s pharmacokinetic research has led to an increasing use of high-dose oral morphine and methadone in cancer patients (Säwe 1986). Keeping in mind the previous abuse experience with these drugs, current prescribing is guided by strict regulations for narcotics.

[1] Injectables that are also available for oral use.
[2] Only available for parenteral use.

Table 1. Narcotic and psychotropic drugs under regulatory control in Sweden.

Schedules II and III	Schedules IV and V	
Fentanyl	Alprazolam	Meprobamate
Hydromorphone	Chloral hydrate	Methohexital[2]
Ketobemidone'	Chlordiazepoxide	Methyprylon
Methadone[1]	Clomethiazole	Midazolam[2]
Morphine[1]	Clonazepam	Nitrazepam
Pentazocine[1]	Clorazepate	Oxazepam
Pethidine	Diazepam	Phenobarbital
Phenoperidine	Flunitrazepam	Pyrithyldione
Piritramide	Hexapropymate	Triazolam
	Lorazepam	

[1] Injectables that are also available for oral use.
[2] Only available for parenteral use.

Drug abuse and dependence have lately attracted much attention and are of major concern to health authorities as well as practitioners. With this has come an awareness of the need for auditing mechanisms and/or control measures at different levels of the health care system in order to promote rational prescribing of drugs with an inherent abuse liability.

This paper will discuss the current epidemiological approaches to these problems in Sweden. Although the term "medication" has been rightly advocated to distinguish drugs used in a medical context fromillicit drugs (Wright 1987), for the sake of consistency with current pharmaco-epidemiological terminology we will continue to use the term "drug" for medically useful substances with abuse liability, even if they might be subject to illegal use.

THE CLINICAL/PUBLIC HEALTH PROBLEM

Prior to marketing, the assessment of abuse liability of drugs, as for any other measure of efficacy (and safety), is conducted under experimental conditions and with populations which do not necessarily reflect the reality of routine medical practice, such as the use of subjects who have had little or no exposure to psychotropic drugs, nor medical conditions requiring use of these drugs. In some cases, experimental assessment has been performed in individuals with previous history of drug abuse. However, drugs may have different effects on different subject populations. For example, it remains to be established that sedative drugs, and

benzodiazepines in particular, have significant reinforcing effects or induce preference in subjects who do not have histories of sedative abuse (Woods et al., 1987). Much information is still lacking on the determinants of the use and misuse of drugs with central nervous system actions and their consequences. Therefore, epidemiological data is needed to place into perspective limited premarketing experimental data.

From the perspective of ensuring the most optimal (safest and most effective) use of drugs, an ongoing auditing process is required (Crooks 1984), particularly for those drugs with abuse liability. Descriptive drug utilization studies are essential as a "signalling" mechanism to draw attention to problems which arise with the drugs with abuse liability, to assess the appropriateness and to quantify the extent of use and misuse. The descriptive approach to the study of drug utilization at all levels of the health and drug chain may be quantitative or qualitative. For example, quantitative studies may describe time course profiles of psychotropic drug usage at different levels of the health care system (national, regional, local, institutional). On the other hand, qualitative studies address the appropriateness of drug use by evaluating it relative to the medical context (indication/condition) and the patient characteristics.

Data derived from such studies, whether quantitative or qualitative, may form the basis for discussions, be it at the national or the local level, the results of which, if appropriately translated into practice, reduce the risk and increase the effectiveness of drug therapy.

THE METHODOLOGICAL PROBLEM

Considerable amount of psychotropic drug use data is currently available. Routine statistics on consumption of drugs have traditionally been compiled either for administrative or marketing purposes. The sales data have been usually expressed in terms of cost or volume units. Although total costs or unit costs (cost per package, tablet, dose, treatment course) may be useful for measuring and comparing the economic impact of drug use, these units do not provide information on the amount of drug exposure in the population. Moreover, cost data are influenced by a number of factors such as price fluctuations over time, distribution channels, inflation, price control measures, etc. (WHO/EURO 1970).

Volume data is also available (overall weight or unit volumes) such as number of packages, tablets, prescriptions, doses, treatments, etc. Drug package sizes may differ in the number of tablets contained from time to time or country to country. Dosage forms may be available in various strengths.

The number of prescriptions is one of the most frequently used units of volume. However, distinction must be made between first prescriptions and refill prescriptions, as they affect the estimate of the number of persons treated or exposed to the drug. Additional problems may be posed by differences in the number of prescription items in each prescription. It should be noted that all these units represent approximate estimates of true consumption, which ultimately is determined by the patient's actual drug intake (degree of compliance).

Aggregate drug utilization data may provide crude estimates of the extent of drug use, but, by themselves do not indicate the quality or appropriateness of use. The appropriateness of drug utilization must be assessed relative to the reasons or medical indications for, or consequences of, drug use (the clinical context). Data on morbidity and mortality may be searched for in national registries (general or specialized, such as toxicology centers, adversedrugreactionsreportingcenters, etc.), national sample surveys; ad hoc surveys and special studies; hospital records; physician records; and patient/household surveys. Some of the morbidity and mortality data may be available, but perhaps not relevant for clinical purposes.

In addition to the reasons for drug use, and particularly in the assessment of drug abuse liability, data is needed on individual patterns of use, such as the frequency of intake (on a daily, weekly, monthly basis), the duration of use, and whether it is on a regular or an intermittent basis.

CURRENTLY AVAILABLE DRUG UTILIZATION DATA BASES

Over the past 20 years, data on drug utilization has been systematically compiled through the use of drug sales statistics, prescription surveys, and continuous recording of prescriptions in two defined geographic areas. Two of the currently available drug databases are linked to morbidity (diagnosis/indication) data. All are potentially useful, despite some limitations, for the study of drug use and misuse.

Total sales of drugs to pharmacies and hospitals have been recorded by Läkemedelsstatistik AB (Swedish Pharmaceutical Data, Ltd. LSAB) since 1965. These sales statistics are published quarterly in the Swedish Drug Market (SDM) and are distributed to subscribers in the pharmaceutical industry, the National Board of Health and Welfare (Department of Drugs), and the National Corporationof Pharmacies (Apoteksbolaget). The sales statistics are also made available by the Department of Drugs of the National Board of Health and Welfare through the online Swedish Drug Information System (SWEDIS). The National Corporation of Pharma-

cies (Apoteksbolaget) publishes annual drug sales statistics for the country as a whole and for each county since 1976. As of this year (1988) national drug sales statistics are provided under the Anatomic-Therapeutic-Chemical (ATC) drug classification recommended by the Nordic Council on Medicines and the World Health Organization (WHO) Drug Utilization Research Group to facilitate comparability in cross-national studies. Comparative drug utilization data for the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) have also been routinely available since 1979 (Nordic Council on Medicines 1979; 1982; 1986; 1988).

A continuous nationwide prescription survey has been conducted since 1974. For each prescription in a sample of 1 in 288 prescriptions filled the following data are recorded: age and sex of the patient, the name and amount of drug prescribed, daily dose, patient fee and total cost (Wessling 1987). Data obtained from this survey have been used to validate the sales data and to provide age and sex profiles, etc., (figure 1).

The Swedish Diagnosis and Therapy Survey is a collaborative project run by the Swedish Pharmaceutical Data Ltd (LSAB), the National Corporation of Pharmacies (Apoteksbolaget), the Swedish Medical Association, and the National Board of Health and Welfare. A random sample of 1 out of 8 physicians (2200 per year) are asked to participate. During a study week all prescriptions are recorded on self copying forms with additional information on the indication or diagnosis for each drug, patient characteristics (age and sex), type of consultation, etc. The diagnoses or symptoms are coded according to the International Classification of Diseases. This survey is similar to IMS America's National Drug and Therapeutic Index (Bergman and Dahlström 1988). The data are analyzed according to IMS routines and provided to subscribers twice a year. Drug utilization data from this ongoing survey are also included in the annual drug statistics published by the National Corporation of Pharmacies (Apoteksbolaget 1988).

In the County of Jämtland Project all drug prescriptions dispensed to 14 percent of the Jämtland population (approximately 17,000) have been continuously monitored since 1970 (Bergström and Westerholm 1973). The recorded information includes the patient unique identity number; name, dosage, quantity, and price of the drug; date of dispensing; dispensing pharmacy; and prescribing physician. This pioneer database has been useful in studying individuals' purchases of psychotropic medication over time. In a six-year longitudinal study of 2566 individuals who purchased hypnotics, sedatives and minor tranquilizers, signs of overuse or abuse were observed in only four patients (0.2 percent) (Boethius and

Westerholm 1977). A number of important issues concerning drug prescribing in primary care have also been studied, such as doses and dosage intervals, prescribing in pregnancy, etc. (Boethius and Sjöqvist 1978; Boethius 1977).

The Community of Tierp Project is run by the Centre for Primary Care Research, University of Uppsala, Sweden. Since 1972 prescription and morbidity data are routinely collected from all pharmacies and the health center within the community for all residents (21,000). The data base has been used to study patterns of psychotropic drug utilization in patients considered as "heavy users" of prescription drugs in general (Isacson and Smedby 1988). However, aggregate drug data are stored on a pharmacologic or therapeutic class basis and, with the exception of the benzodiazepines, it is not possible to study individual drugs.

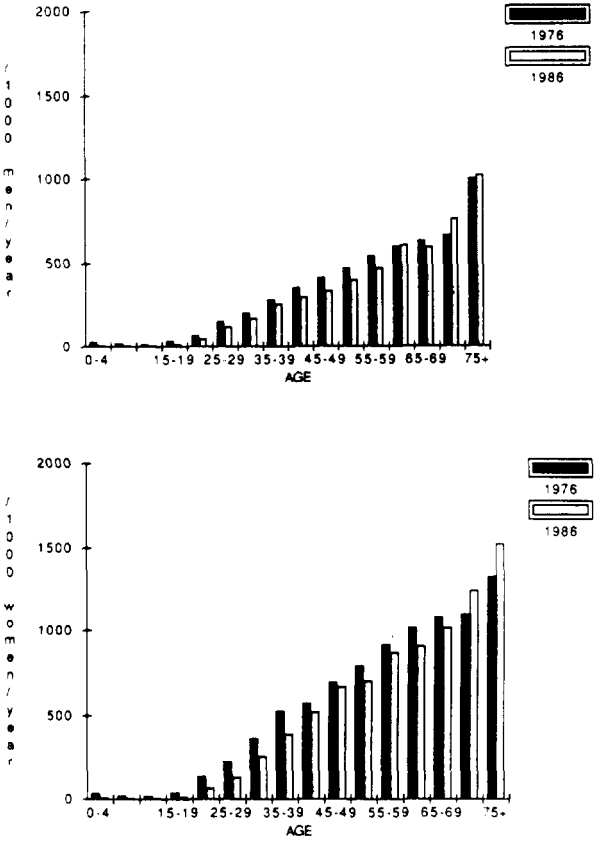

Figure 1: *Hypnotics, sedatives and minor tranquilizers. Age and sex distribution of prescription items per 1000 men (upper) and 1000 women (1ower) per year in 1976. and 1986 (Permission to reprint from Bergman et al., 1988:4. granted by B-E Wiholm, Dept. of Drugs, National Board of Health)*

Interestingly, in these two independent databases a marked decrease in the prescribing of hypnotic-sedatives and minor tranquilizers has been observed since the early 1970s. The decrease was most prominent in the proportion of the population with infrequent prescription of these drugs, whereas the proportion with regular use appeared to be stable (Boethius and Westerholm 1979; Isacson and Smedby 1988).

The small size of both of the above databases are important limitations for hypothesis testing studies, as evidenced by recent unsuccessful efforts to confirm or refute the signal generated by Laegreid et al. (1987) concerning the teratogenicity of benzodiazepines (Bergman et al., 1989).

Units of Measurement

Two standard units have been developed in the Nordic countries to measure and compare drug utilization and have been widely used in the past 15 years. Although the number of prescriptions is also widely used, the following discussion will be limited to the Defined Daily Dose (DDD) and the Prescribed Daily Dose (PDD).

The Defined Daily Dose methodology was developed in the 1970s to standardize and exploit readily available volume data from sales statistics or pharmacy inventory data (quantity of packages, tablets or other dosage forms). Drug sales data was converted into medically meaningful units, to make crude estimates of the number of persons exposed to a particular drug or class of drugs (Baksaas-Aasen et al., 1975; Bergman et al., 1979). The defined daily dose (DDD) is the assumed average maintenance dose for the main indication of a particular drug. Expressed as DDDs/1000 inhabitants/day it can be interpreted as the proportion of the population that may receive treatment with a particular drug (Baksaas-Aasen et al., 1975; Nordic Council on Medicines 1986). Figure 2 illustrates the trends in sales of hypnotics, sedatives, and minor tranquilizers, expressed in DDDs.

For use in hospital settings, it may be expressed as DDDs/100 bed-days (adjusted for occupancy rate) (Bergman et al., 1980). The method has been useful in describing and comparing national and international patterns of psychotropic drug utilization (Grimsson et al., 1979; King and Griffiths 1984), providing denominator data for the estimation of rates of reported adverse drug reactions (Bergman et al., 1978), epidemiologic screening for problems in drug utilization (Westerholm 1986), and to monitor the effects of informational and regulatory activities (Sjöqvist 1975; Lunde et al., 1987). The advantages of this methodology include: its usefulness for working with readily available gross drug statistics at

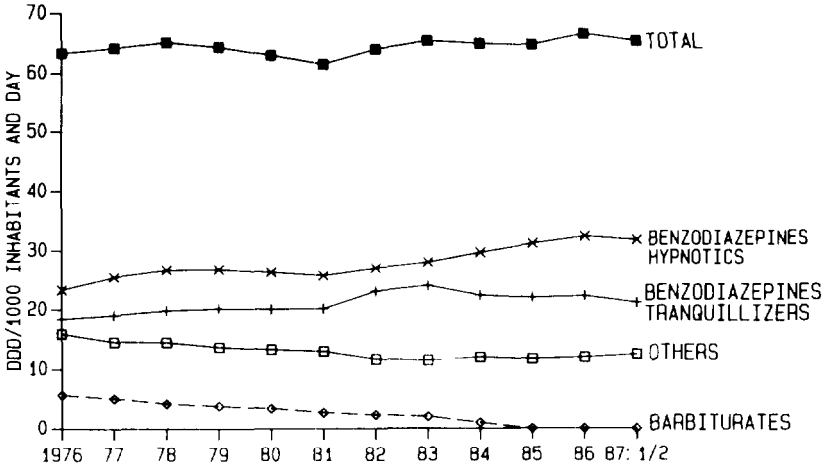

Figure 2: *Sales of hypnotics, sedatives and minor tranquilizers in Sweden, 1976 July 1987, expressed in DDDs/1000 inhabitants/day (Permission to reprint from Bergman et al., 1988:4, granted by B-E Wiholm, Dept. of Drugs, National Board of Health).*

various levels of the drug and health chain; as a standardized unit of measurement, it allows comparisons between drugs in the same therapeutic class, between different health care settings or geographic areas, and comparisons over time; and is relatively inexpensive. The DDD methodology has, however, some important limitations. The DDD is not a recommended dose, but rather a technical unit of comparison. Since DDDs are based on usage in the Nordic countries, some DDDs may be high or low relative to other countries. Many drugs that are not marketed in the Nordic countries have not been assigned DDDs (but guidelines have been published for defining DDDs under these circumstances) (Nordic Council on Medicines 1982, 1986). Additional problems arise when dosages vary according to its indication as in the case of the neuroleptics, or when drugs are used in combination with other drugs for the same disease. Although in Sweden, the use of psychotropic drugs in analgesic and other combination products ("hidden psychotropics") is not a problem, this may be of importance in countries with elevated utilization of combination drugs (Laporte et al., 1981). Moreover, the DDD does not take into account pediatric uses. Since children's doses are substantially lower than the established DDDs, this situation will lead to an underestimation of population exposures which may be significant in countries with a large pediatric population.

The prescribed daily dose (PDD) is another unit, developed as a means to validate the DDDs. The PDD is the average daily dose prescribed, as obtained from a representative sample of prescriptions (Bergman and Sjöqvist 1984). This unit provides a closer estimate of drug exposure. Close agreement between the DDD and the PDD has been demonstrated for drugs such as diazepam, nitrazepam, and clorazepate, whereas major discrepancies were observed with other benzodiazepines and the neuroleptics (Bergman and Sjöqvist 1984). Higher PDDs have been observed in the U.S. relative to Sweden for commonly prescribed drugs, such as diazepam and oxazepam (Bergman and Dahlström 1986). The comparison indicated that even though population exposure is higher in Sweden than in the U.S., Americans are prescribed higher daily doses of benzodiazepines (Bergman et al., 1986). Although the DDD and the PDD may be used to estimate population drug exposure, the methodology is not useful to quantify or identify patients who receive doses lower or higher than those considered effective and safe or sequential changes in dosage.

CLINICAL AND ADMINISTRATIVE SOURCES OF INFORMATION

A variety of different sources of information are available to provide a clinical context to drug utilization data. Most hospitals in Sweden have a computerized register of discharge diagnoses which allows a retrieval of medical records according to specific diseases. Autopsy records and analyses from the toxicology laboratories and the national toxicology information center have been used in studies of psychotropic drug use and abuse (Allgulander et al., 1984; Melander et al., 1984).

The Swedish Spontaneous Adverse Drug Reaction Reporting System was established in 1965 at the Department of Drugs of the National Board of Health and Welfare. Since 1975 it has been compulsory to report suspected reactions that are fatal or otherwise serious, as well as new and unexpected reactions. The annual rate of reporting has gradually increased over the years (Strandberg and Wiholm 1986). Abuse and dependence, however, are rarely reported as side-effects of drugs (0.5 percent). Based on the WHO Collaborating Centre for International Drug Monitoring, even on a global basis drug abuse/dependence account for only 0.6 percent of all reports up to 1986 (Bergman 1986).

The National Board of Health and Welfare has periodically conducted one day prevalence studies on inpatient psychiatric diagnoses. The latest survey in 1985 revealed that drug abuse was diagnosed in 5 per 1000

hospitalized patients. Hypnotics and sedatives were associated with 91 percent of these hospitalizations, barbiturates (in the process of being withdrawn from the market) 3 percent, and analgesics 6 percent (Bergman 1986).

The Stockholm County Council, covering 1.5 million inhabitants, has conducted a continuous register of hospital discharge diagnoses since the late 1960s. Surveys covering the 1970s and 1980s indicate that one per 1000 residents have been hospitalized with the diagnosis of drug abuse (Bergman 1983; Bergman et al., 1988). In the survey covering 1969-1982, one-third of the patients (n=729) had no such history of alcohol or illicit drug abuse. Two-thirds of these patients were women. In 24 percent of the cases barbiturates were involved, in 67 percent other hypnotic-sedatives, and analgesics in the remaining 9 percent. The results of longitudinal analyses indicate a high degree of morbidity (hospitalizations for somatic and/or psychiatric problems) and mortality, consistent with findings from another detailed follow-up study in the same catchment area (Allgulander et al., 1984).

Prescription forgeries and theft/loss reports may be a useful indirect (proxy) measure of misuse and abuse. All outpatient pharmacies (800) are administratively organized in six pharmacy regions within the National Corporation of Pharmacies (Apoteksbolaget AB). Prescription forgeries uncovered at the outpatient pharmacies within each region are periodically reported (twice a year) to the Department of Drugs, National Board of Health and Welfare. Data in the reports include the name of the drug(s) in the prescription, the date and dispensing pharmacy. Similarly, theft and loss reports from drug distribution channels (pharmacies, general/family practices, clinics, hospitals, etc.) are reported to the Department of Drugs through the regional pharmacy centers. The results of a study comparing the rates of reported prescription forgeries and theft/loss reports for diazepam and oxazepam were consistent with experimental data in humans (Griffiths et al., 1984) that suggest a higher abuse liability for diazepam relative to oxazepam (figure 3). The difference in rate of reports was still significant when the most widely known brand of diazepam (Valium) was excluded from the calculations (Bergman and Griffiths 1986). This approach may be useful in a drug abuse surveillance network. When prescription forgeries and theft/loss reports are related to actual drug utilization, the changes in prevalence and patterns of abuse may suggest problems that merit indepth investigation (Bergman and Dahl-Puustinen 1988). An important issue to be considered in the interpretation of the data generated is the rate of detection and reporting of prescription forgery. At present, accurate data on rates of detection and reporting of

prescription forgeries is not available. The extent of use of prescription forgeries and theft to obtain drugs, relative to consulting physicians for a prescription, must also be taken into consideration in the analysis of these data.

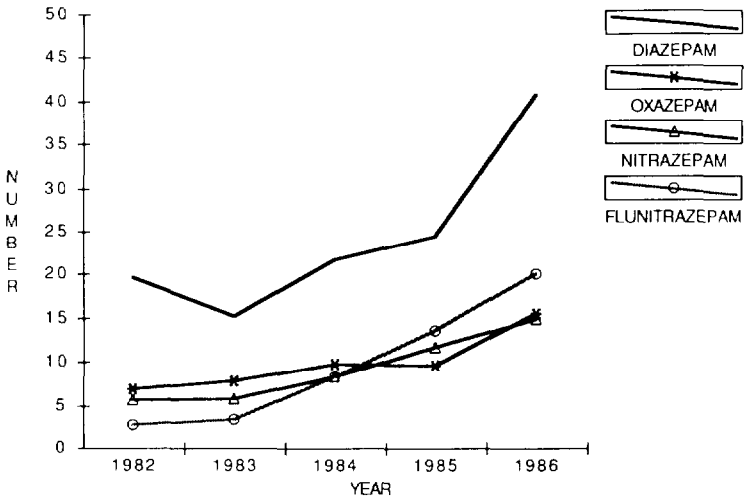

Figure 3: *Relative prescription forgeries per 100,000 prescription items for the four major benzodiazepines in Sweden, 1982-1986. (Bergman and Dahl-Puustinen 1988)*

INTERVENTION STRATEGIES BASED ON DRUG UTILIZATION DATA

Current activities to promote the rational use of drugs with abuse potential in Sweden fall under a more comprehensive approach to rational drug utilization, emphasizing information and education, self-auditing, and, on occasion, regulation.

Drug utilization data are important elements in the expert discussions and formulation of consensus statements which have been conducted as a workshop series by the National Board of Health and Welfare since 1982, and have recently included discussions on the pharmacological management of alcohol abstinence, anxiety, and sleep disorders (Drug Information Committee 1985:2; 1988:1,4).

Drug utilization data, in the form of trends in overall sales statistics and prescribing patterns, are routinely published (Svensk Läkemedelsstatistik 1987) and made widely available to stimulate and facilitate discussions at all levels of the health care system, particularly in local or regional therapeutics committees.

Two examples may serve to illustrate the Swedish approach regarding drugs with abuse potential and the role of drug utilization data in drawing attention to potential or actual problems of misuse or abuse.

In 1983, dextromethorphan was changed from prescription to over-the-counter (OTC) status. Concurrent with an increase in sales, several local outbreaks of dextromethorphan abuse in young people were reported over a 2 year period (Swedish Adverse Drug Reactions Advisory Committee 1985). In 9 of 30 surveyed areas belonging to a nationwide drug abuse surveillance network, it was established that most of the outbreaks were self-limiting and of short duration. However, although overall dextromethorphan sales had decreased considerably, in two areas the abuse level increased and extended to the adult population, as determined from reports by the network and various other sources (police, schools) and queries received by the national poison information center. The use of much higher doses of dextromethorphan which were associated with abuse may explain why results on liability testing were negative in humans using low doses as opposed to positive results in animal studies (Griffiths and Balster 1979). This risk was judged to be unacceptable for an OTC drug and dextromethorphan was placed, once again, on prescription status in April 1986 (Socialstyrelsens läkemedelsavdelning 1986).

In 1978, local review of the routinely published sales statistics for hypnotic, sedatives and minor tranquilizers revealed that sales in Malmöhus county were well above the national mean. The follow up investigation indicated that most of the prescribing was limited to the city of Malmö and the very high prescribing rate to a small number of physicians (Kaij et al., 1983). The appropriate indications for these drugs were reviewed in a scientific meeting held in Malmö in 1979 and an information letter by the local medical association was sent to all physicians discussing the precautions to be taken in the prescribing of these drugs. The sales of these drugs decreased following these information activities. Parallel decreases in the number of hospitalizations due to abuse of these drugs and the number of lethal barbiturate intoxications were observed (Melander et al., 1984). The effect on the drug sales and number of hospitalizations, however, was short-lived as shown by subsequent rises (Melander and Stenberg 1986). Figure 4 illustrates the decrease and subsequent rise in

sales of these drugs in the larger area of Malmöhus county. The unfavorable risk/benefit of the barbiturates derived from these and other observations in the Stockholm area resulted in the withdrawal of the oral forms of barbiturates (with the exception of phenobarbital for epilepsy) from the Swedish market (Socialstyrelsens läkemedelsavdelning 1984).

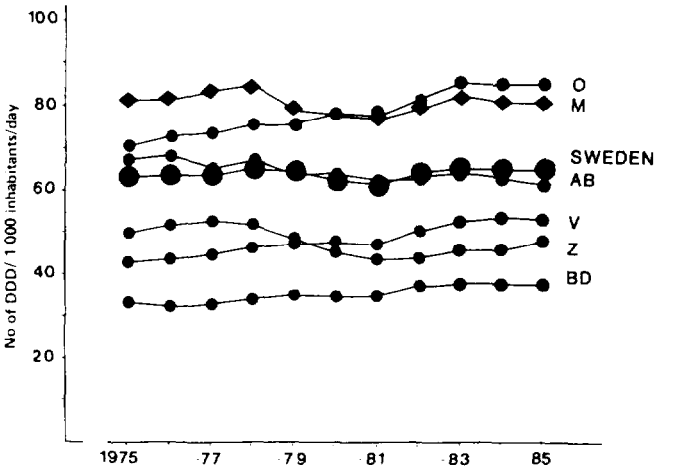

Figure 4: *Sales of hypnotics, sedatives and minor tranquilizers in selected counties of Sweden, 1975-1985, expressed in DDDs/1000 inhabitants/day. M = Malmöhus county; O = Gothenburg and Bohus; AB = Stockholm; Z= Jämtland; V = Västmanland; BD = Norrbotten (Permission to reprint from Bergman and Dahlström 1988:1) granted by B-E Wiholm, Dept. of Drugs, National Board of Health).*

THE FUTURE

Opportunities

The descriptive epidemiological study of the use of drugs with abuse liability has primarily focused on the quantification of the extent of use in the context of a more comprehensive signalling system that covers all marketed drugs. Any "signalling" or "hypothesis generating system" may also require some form of "hypothesis testing system" to be able to provide meaningful conclusions. With regard to abuse liability testing, this is probably best done in human experimental studies. It has been suggested that the abuse potential of new drugs relative to well known drugs on the market ought to be part of the registration dossier for relevant psychotropic and analgesic drugs (Bergman et al., 1988:4).

Some initial work has been done regarding individuals' use of psychotropic drugs over time with the availability of patient specific drug databases. Further studies investigating the determinants, patterns, risks and conse-

quences of the long-term use of drugs with abuse liability, alone and in combination with other drugs, are warranted. Research is also sorely needed on the absolute and relative efficacy of the various interventions that have been proposed to reduce the risk of dependence development (Woods et al., 1987). This may be facilitated with the development of larger databases (greater population coverage) and linkage to morbidity and mortality data or primary physician records.

The further development of patient specific databases may facilitate not only descriptive, analytical, and experimental epidemiological studies, but also to incorporate the studies in the context of timely identification of individuals at risk of developing drug dependence and preventing or treating those who actually do ("drug shoppers"). The use of patient specific drug histories linked to morbidity information to signal potential drug therapy related problems is an essential element in novel intervention programs (therapeutically oriented drug utilization review) already established in some parts of the United States (Groves 1985; Strom amd Morse 1988).

Problems

Historically, the large medical and pharmaceutical computer databases have been established primarily for purposes other than scientific study. All relevant information may not be available from the various databases and access to primary records will necessarily be required for valid epidemiological studies. These limitations have to be taken into account in the design of proper epidemiological studies.

Although the technical aspects of ensuring the confidentiality of patients' medical and pharmaceutical records in computer databases have been successfully handled in other settings, the ongoing debate over the confidentiality issue in Sweden has impeded the capture of patient specific drug data or its current use in health services research.

The development of a specific signalling system for drugs with abuse liability has also been affected by legal and confidentiality issues. Local units participating in a "drug abuse surveillance network" advocated by the Swedish National Board of Health and Welfare in 1981, have been implemented at a number of places in Sweden. This was found to be a valuable way of integrating issues concerning drug abuse into the local health care organization (Bergman et al., 1988b). These members, representing the in- and outpatient services as well as the local pharmacy, integrated local prescribing data with data on abuse obtained from sources such as the emergency room, the intensive care unit (Gustafsson et al.,

1988), laboratory analyses, as well as questions posed to the drug information center, to provide the best available health care for the individual patient with potential drug dependence problems in the catchment area. However, legal requirements and interpretations of informed consent have limited the functioning of this network.

The increasing interest in cost-containment and cost-effectiveness issues, which are also present in Sweden, may become an influential factor in future approaches to the study of drug use and misuse.

CONCLUSION

The epidemiological study of use and misuse of drugs with abuse liability in Sweden has been developing within the wider context of drug utilization in general. A number of methods and standardized units of measurement are currently employed, which are based on relatively inexpensive and readily available sources of drug statistics. Computer databases which facilitate longitudinal studies, albeit limited in size and data elements, have also contributed to the study of drug use and misuse. Drug utilization data are essential elements of ongoing therapeutic audits performed at various levels of the health care system. The experience so far has been quite limited, particularly with regard to drugs with abuse liability. Much more research is needed on the development of abuse, the determinants, patterns, risks, and consequences of the long-term use and misuse of these drugs. Various approaches to reducing the risks and consequences of misuse and abuse of drugs may be relevant and should be rigorously assessed. At present, the political issue regarding confidentiality of medical records and prescriptions seems to be the most important determinant of the future epidemiological study and development of methods to measure, and strategies to reduce, the risks of drug use, misuse, and abuse.

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CHAPTER 14

Pharmacokinetic and Pharmacodynamic Drug Interactions: Implications for Abuse Liability Testing

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INTRODUCTION

Every time two or more psychotropic drugs are ingested concurrently, they will interact in some biochemical, physiological or pharmacological fashion. Fortunately, most such interactions are unimportant events. The important consequences of psychotropic drug interactions include the following: an unexpected or unpredictable degree of impairment in performing daily tasks associated with a serious potential for injury (e.g., driving a car, operating machinery); accidental death from overdose; the augmentation of behavioural toxicity above that for the drugs alone (e.g., cognitive functions; violent behaviour, impaired formation of intent or recognition of the consequence of one's action, impaired memory acquisition, retention or recall); and altered abuse liability.

The literature relating to psychotropic drug interactions is vast; however, much of it is of limited value because it focuses on the hazards of acute toxicity of such interaction and the relevance to abuse liability is only by inference. Many reviews of such drug interactions exist (Grahame-Smith 1977; Haratzi and Davis 1978; Sellers et al., 1983). The interaction of alcohol with other psychoactive drugs has been extensively studied and reviewed (Linnoila et al., 1979; Mattila 1979; Sellers 1979, 1984; Sellers et al., 1980a; Sellers and Busto 1982).

The complexity of abuse liability testing for single abusable drugs is further compounded when more than one drug is present. Drug doses. duration of use and order of administration increase the experimental possibilities markedly. For example, at least three general combinations of drug administration are relevant: 1) acute ingestion of single doses of the two drugs; 2) chronic use of each drug plus a single dose of the other

drug; and 3) chronic use of each drug together. For each of these combinations, the at-risk populations need to be specified, e.g., drug abusers, therapeutic users, general population. Finally, qualitative and quantitative changes in drug effect (pharmacodynamics) can be further confounded because drugs can alter each other's disposition (pharmacokinetics) (figure 1) (Ross and Gilman 1985).

In order to fully characterize a drug interaction "surface," multiple doses (ideally plasma free drug or biophase concentrations of the drug), sequences, routes of administration and durations of administration or therapy with each drug alone and together are necessary (Loewe 1953). Theoretically, such interaction surfaces can be discontinuous; however, this theoretical prediction has not yet been borne out in practice (Carpenter 1975). The increasing specificity and selectivity of drugs, however, increases the likelihood such phenomena will be found.

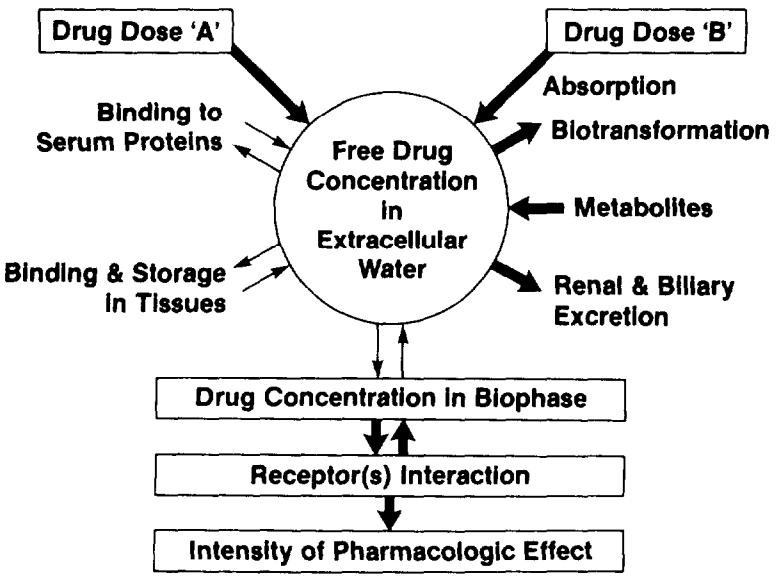

Figure 1: *Mechanisms of pharmacokinetic interaction and relationship of drug dose and effect.*

POTENTIAL FOR DRUG INTERACTIONS IN ABUSING POPULATIONS

The assessment of abuse liability requires identification of the at-risk population. Theoretically, the risk of abuse is assumed to increase as one progresses from the general population, to therapeutic users, protracted therapeutic users, abusers of a single drug within the pharmacologic class, to multi-drug abusers. The assessment of abuse liability of new drugs requires conducting studies on representative samples of the at-risk individuals. Most studies do not provide systematic validated concurrent and past-drug use/abuse history about their subjects, hence the appropriateness of the sample and its generalizability to the at risk abuse population is uncertain. For practical reasons, abuse liability testing is typically conducted in small numbers of compliant volunteers.

Table 1 summarizes the pattern of current substance abuse diagnosis in discharged patients identified on the basis of the index diagnosis of benzodiazepine abuse Diagnostic and Statistical Manual (DSM-III). The patterns of tobacco and caffeine use or abuse are not known in these individuals. Eighty-six percent (271/314) of such discharged patients abused at least one other drug hence patients discharged with a diagnosis of benzodiazepine abuse frequently have other concurrent abuse disorders.

Table 1. Most common other drugs of abuse in 314 consecutively admitted benzodiazepine abusers (1978-1984)

Drug	Mentions (N)	Admissions (%)
1. Ethanol	142	45
2. Cannabis	82	26
3. Codeine	81	26
4. Oxycodone	64	20
5. Secobarbital	43	14
6. Amphetamine	39	12
7. Heroin	35	11
8. Butalbital	30	10
9. LSD	25	8
10. Cocaine	23	7

Total Mentions = 922

Within the benzodiazepine abuse population the age and sex distributions of pure (i.e., only benzodiazepine), primary (i.e., most responsible drug) and non-primary (i.e., secondary importance) benzodiazepine abuse populations differ (figures 2 and 3).

These data indicate that at a descriptive level drug abuse patterns are complex and that interactions are common. Table 2 presents the pattern of benzodiazepine use in chronic alcoholics (Busto et al., 1983). Benzodiazepine use is common among in-patient and out-patient alcohol, methadone, cocaine and amphetamine users (Woody et al., 1975; Stitzer et al., 1981). With respect to assessment of abuse liability for drugs, the labelling of such individuals as cross-dependent is not helpful since it begs the question of prior use and exact order of use as a risk factor. Careful studies of interactions would yield useful information with respect to prevention, treatment and relapse prevention and would yield a better understanding of the degree of interface between pharmacologic events and drug-taking behaviour.

Table 2. Benzodiazepine Use in Alcoholics

	TOTAL N	USING BENZODIAZEPINES N	(%)[1]
Male	200	58	(29)
Female	61	29	(47)

Note: Objective confirmation of benzodiazepine use by urine screen
[1]$p<0.0005$ for differences in proportion between the two sexes

PHARMACODYNAMIC INTERACTIONS

Alterations in the perceived pharmacologic effects (figure 4, upper row) or their behavioural consequences (figure 4, lower row) are the pharmacodynamic interactions important for abuse liability testing. Abuse liability prediction usually focuses on directly measurable pharmacologic features of the drug (figure 4, upper row). The consequent behaviours are postulated to be the interactive consequence of drug effects and antecedent

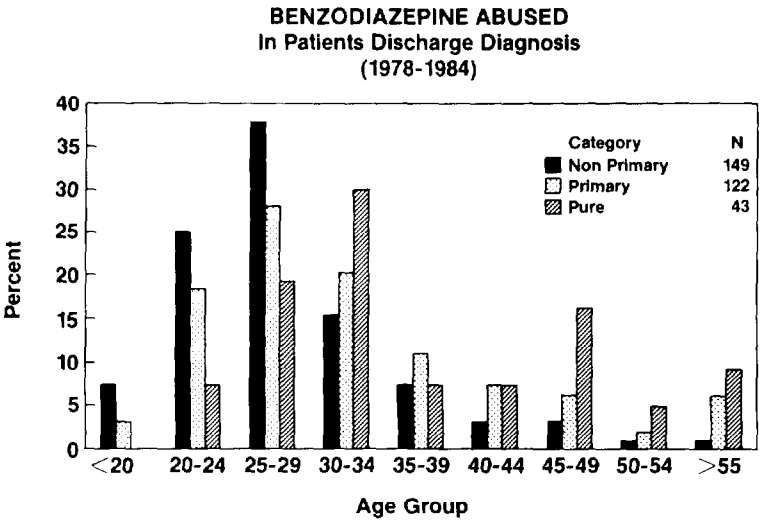

Figure 2: Age distribution of pure, primary and non-primary benzodiazepine abusers.

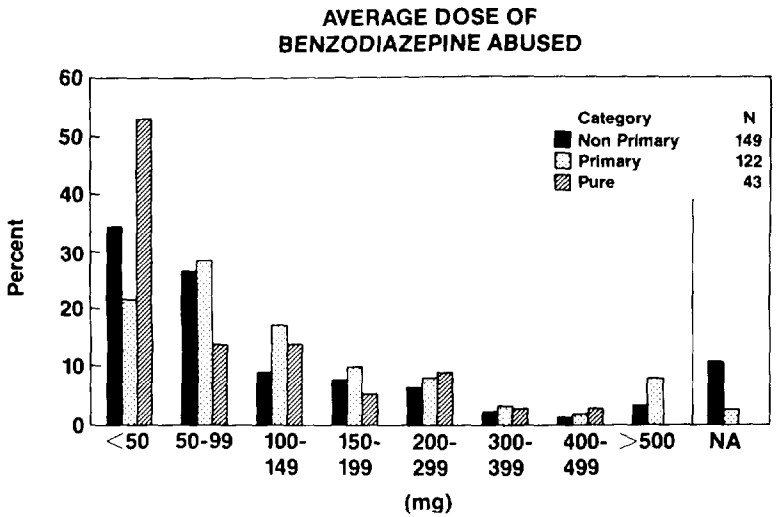

Figure 3: Drug dose distribution as diazepam equivalents of pure, primary and non-primary benzodiazepine abusers.

behaviours (Schuster et al, 1981). Some are clinically observable, e.g. dose escalation (left column), others are more experimental in nature (right column). Discriminative stimulus studies are the basis for inferring the generalizability of the effect of pharmacologic cues on behaviours (Schuster et al., 198 1). Studies in laboratory animals indicate that acute and chronic prior administration of drugs within a class causes cross-tolerance on a variety of motor, autonomic, cognitive and other drug effects (Kalant et al., 1971). Some such changes involve metabolic tolerance (Kalant et al., 1976; Khanna et al., 1976), but most appear to be primarily the result of changes in CNS sensitivity. Hence kinetics, drug effects and behaviours are modified by drug interactions.

In humans, systematic studies of the effects of graded doses of one drug on the measured drug effects and behaviours of interest in abuse liability testing have rarely been done. Mechanistically, such studies are important if we want to know if prior use of a drug increases or decreases the likelihood that a new substance will be abused (i.e., behavioural consequence). From a drug interaction perspective the behavioural, pharmacologic and pharmacokinetic interactions among drugs and their importance to initiation or maintenance of drug abuse or its successful treatment are largely unknown.

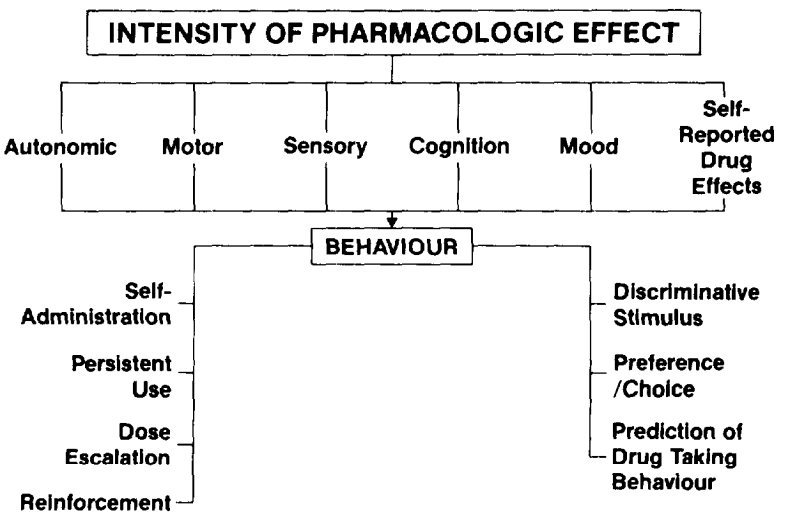

Figure 4: *Drug effects and consequent behaviors affected by drug interactions.*

PHARMACOKINETIC INTERACTIONS

Pharmacokinetic properties of a drug may contribute to abuse liability, drug preference and persistent drug use (figure 1). These kinetic features can be divided into those that relate primarily to acute drug effects (e.g., dysphoria, euphoria, liking, choice, etc.) (Griffiths and Balster 1979; Griffiths et al., 1980; Busto and Sellers 1986) and to the development of physical dependence and post-drug discontinuation symptoms cf. "withdrawal" (Lukas and Griffiths 1982; Busto and Sellers 1986). Each of these can be affected by concurrent administration of other drugs (Sellers and Busto 1982; Busto and Sellers 1986).

Absorption and Distribution

Rapid delivery of a drug to the brain will provide optimal conditions for reinforcement and drug readministration (Arendt et al., 1983; Greenblatt et al., 1983; Bustoand Sellers 1986; Ator and Griffiths 1987). Drugs with highest abuse potential typically have rapid access of an active form of the drug to their site of action in the brain. Pro-drugs such as halazepam, prazepam or flurazepam are slowly converted to active drug and this is thought to account, in part, for their lesser abuse (Jaffe et al., 1983; Griffiths et al., 1984). Therefore, route and rate of absorption tend to shape patterns of drug abuse. In the case of oral administration, concurrent drugs that increase dissolution rate, accelerate stomachemptying, increase systemic bioavailability, or decrease intravascular metabolism (e.g., acetylation, esterases), decrease binding to serum proteins or increase rate of brain entry will all favour increased subjective liking (or aversive experience). Conversely, drugs that decrease gastric acidity, delay gastric emptying (e.g., opiates) or increase protein binding would be expected to decrease drug effects.

The study of early absorption and distribution interactions may require very frequent blood sampling and the ability to measure drug effects rapidly (Sellers and Busto 1982). Drugs administered intravenously or via the lungs require especially frequent sampling to capture the intravascular mixing phase of the interaction (Sellers and Koch-Weser 1969; Koch-Weser and Sellers 1971).

Pre-Systemic Hepatic First-Pass Drug Interaction

Theoretically, drugs with low bioavailability and high hepatic clearance may be expected to be susceptible to the pre-systemic effects of prior administered drugs (e.g., ethanol) (Wilkinson and Shand 1975; Sellers and Busto 1982). The hypothesis that high extraction drugs are particularly

susceptible to ethanol effects has been tested with a number of drugs (Sellers et al., 1980b, 1985; Dorian et al., 1983; 1985). For example, studies in the isolated perfused rat liver indicate that ethanol affects the initial rapid uptake phase into the liver and inhibits subsequent biotransformation of propranolol, a high extraction drug, to its metabolites (Dorian et al., 1984). Such studies suggest that the timing of the presentation of ethanol could be important to the type and extent of pharmacokinetic interaction. The unique positioning of the liver between gut and systemic circulation means that drugs passing through the liver primed by ethanol will be affected by inhibition of oxidative drug metabolism, inhibition of uptake and binding within the liver, changes in liver blood flow or a combination of these factors (Sellers et al., 1980b). Cimetidine, which also inhibits P_{450}-mediated drug biotransformation and decreases liver blood flow, causes an increase in the plasma concentrations of lidocaine and diazepam during the distribution or absorption phase.

However, even "low extraction" drugs can demonstrate that they are susceptible to a pre-systemic absorptive phase interaction with ethanol. Ethanol, for example, causes a 96 percent relative increase in diazepam concentration at 18 minutes after intravenous administration and a 100 percent increase 15 minutes after oral diazepam administrationcompared with a diazepam-alone condition (MacLeod et al., 1977; Sellers et al., 1980a; Sellers 1984). The intravenous data are particularly interesting since they reflect the impact of altered hepatic clearance on a drug during its plasma and tissue distribution phase. After intravenous administration of drug, altered hepatic clearance of drug can be important during the distribution phase because of the high relative blood flow to liver (i.e., approximately 25 to 30 percent of cardiac output) (Sellers et al., 1980b).

Therefore, the influence of ethanol and other inhibitors of drug metabolism or hepatic uptake on pharmacokinetics of drugs can be best understood by considering three overlapping phases: systemic absorption, distribution and elimination.

Physical Dependence and Discontinuation Symptoms

The rate of appearance and severity of withdrawal symptoms depends upon the balance of those factors which determine the degree of physical dependence and apparent rate of drug removal from its site of action. The removal of drug can be due to metabolism. excretion or displacement by an antagonist. The longer a drug's half-life (i.e., high volume of distribution and low total body clearance), the greater the likelihood of the development of physical dependence. The shorter the half-life, the earlier and more

severe will be the withdrawal (Busto and Sellers 1986; Busto et al., 1986; Cappell et al., 1987).

Antagonists are the most dramatic way of shortening a drug's half-life in the biophase. As a result they have an important diagnostic role in establishing the presence of physical dependence in laboratory animals and humans (Lukas and Griffiths 1982). For example, Ro15-1788 precipitates withdrawal from benzodiazepines in baboons and humans. Similarly, naloxone and other opiate antagonists and partial agonists do the same for opiates. Such interactions dramatically unmask the underlying adaptive changes,

Increasing Half-Life, Decreasing Clearance

A number of drugs consistently decrease drug biotransformation by hepatic cytochrome enzymes and prolong half-life, e.g., disulfiram, cimetidine, acute ethanol, chloramphenicol, oral contraceptives (Sellers 1984; Murad and Gilman 1985). For example, caffeine half-life is 10.4 hours in women on oral contraceptives compared to 4 hours in female controls. The clinical importance for caffeine abuse and liability testing is uncertain.

A decrease in total clearance will be associated with a proportionate increase in average steady state free drug concentration if dose is kept constant (Benet and Sheiner 1985). However, if dose has been "titrated" by the subject to a preferred plasma drug concentration it is conceivable that the ingested drug dose may be decreased by a decrease in drug clearance. Such an interaction then could become part of a treatment approach (Bendayan et al., 1988). For high first-pass drugs, inhibitors can also be expected to increase systemic bioavailability after oral administration. Greater effects from single doses can be expected. With respect to the longer half-life (assuming the volume of distribution is constant), the inter-dose area under the curve (AUC) is increased by decreased clearance and fewer inter-dose withdrawal symptoms should occur. Upon discontinuation a more delayed, and less severe set of symptoms should occur. To the extent such symptoms are a cue or trigger for persistent drug use, drug use should decrease (Busto and Sellers 1986).

Decreasing Half-Life, Increasing Clearance

Phenobarbital, chronic ethanol, tobacco smoking, rifampin or carbamazepine can double or triple total clearance of some abused drugs (Murad and Gilman 1985). The consequent shortening in half-life and decrease in average steady state drug concentration should be associated with some or all of the following: a decrease in drug effect (unless the

metabolites are more active or toxic than the parent compound), a decrease in total and free drug concentration; a compensatory increase in drug dose self-administered; shortening of the dose interval; an increase in number and severity of withdrawal symptoms and greater difficulty in discontinuing drug. Once again, the clinical importance of such phenomena is unknown. Of these, heavy smoking deserves particular attention (Sellers et al., 1983). The biotransformation of caffeine, nicotine and other xanthines may be affected by smoking and enzyme induction. The extent of interindividual variation in caffeine "tolerance" and discontinuation symptoms may in part be explained by confounding co-drug use, e.g., ethanol, smoking, barbiturates, etc.

EXPERIMENTAL EXAMPLES

The interactions of ethanol with several drugs will be used to illustrate the specific principles reviewed above.

Acute Ethanol Ingestion and Single Doses of a Benzodiazepine

Diazepam absorption may be delayed slightly if alcohol is given 30 minutes before the dose of diazepam. The apparently slight differences in order and timing of drug and ethanol administration may explain other discrepancies among reported studies of the ethanol-diazepaminteractions (Sellers and Busto 1982; Sellers 1984).

MacLeod and associates showed that 0.5 g/kg of ethanol in a 20 percent v/v oral solution resulted in diazepam levels about 30 percent higher after ethanol than with diazepam alone, although the increases were not as great when the alcohol and diazepam were co-administered (MacLeod et al., 1977). No significant changes in diazepam absorption rate or plasma elimination rate were found up to 8 hours post-drug. Since the bioavailability of diazepam is normally high, the observed increase in peak diazepam could arise from an ethanol-mediated decrease in initial diazepam distribution volume. This possibility is attractive because ethanol is metabolized relatively quickly compared with diazepam; hence, any acute ethanol-mediated effects are transient and occur during a phase of diazepam disposition characterized and predominated by absorption and tissue distribution.

A balanced cross-over study confirmed that ethanol increases concentrations of intravenously administered diazepam by inhibiting the hepatic intrinsic clearance of free diazepam and altering diazepam and desmethyldiazepam free fraction (Sellers et al., 1980a). These observations

clarify the pharmacokinetic mechanism of ethanol-diazepam interaction and suggest that a similar mechanism accounts for changes in disposition with other benzodiazepines.

Chronic Ethanol Ingestion and Benzodiazepines

Considerable basic pharmacological research suggests that acute ethanol exposure inhibits microsomal mixed function oxidase activity (see preceding section) and chronic administration stimulates drug metabolism (Sellers et al., 1983).

In recently abstinent chronic alcoholics, the peak and AUC for diazepam are lower after oral diazepam than in control subjects (Sellman et al., 1975a). Whether these results are due to a decrease in serum albumin with an increase in the volume of diazepam distribution, decreases in bioavailability or increased biotransformation is not known because half-life could not be accurately estimated with the limited number and brief period of diazepam blood level measurements. A comparable study in chronic alcoholics given intravenous diazepam also showed decreased peak diazepam and AUC up to 12 hours post-dose and lower desmethyldiazepam levels, suggesting an increased initial volume of distribution (Sellman\] et al., 1975b).

Sellers and colleagues (1978) reported the pharmacokinetics of chlordiazepoxide during alcohol withdrawal in six male chronic alcoholics (defined as individuals who ingested more than 80 g of ethanol per day for at least 10 years). These subjects received 25 mg of chlordiazepoxide every 6 hours for 6 days. Steady state plasma levels of chlordiazepoxide were decreased on day 6 compared to levels on day 2 of withdrawal, suggesting increased chlordiazepoxide clearance. This is consistent with a return to normal enzymatic activity after the inductionof mixed function oxidase enzymes.

Interpretation of these studies is difficult because of concurrent changes in drug free fraction (Greenblatt et al., 1982; Sandor et al., 1983). Increased free fractions caused by fatty acids or competing drugs will decrease the average stated state drug concentration in plasma. The net free drug concentration may be unchanged (Greenblatt et al., 1982). However, important enhancement of effect based on high free concentration can occur during the acute distribution and inter-dose distribution phase (Sellers 1986).

The clinical consequence of an increased drug clearance is that patients will have a lower average steady state drug level and a lesser therapeutic

or toxic effect. The clinical implication of increased benzodiazepine clearance is further confused because there is cross-tolerance between ethanol and benzodiazepines, suggesting that chronic ethanol ingestion might not only decrease blood levels but also decrease central nervous system sensitivity to the benzodiazepines. Of course, the typical pattern of ethanol ingestion is alternatively intoxication and abstinence so that a fluctuating mixture of kinetic and dynamic effects can be predicted in the usual field setting.

Acute Amitriptyline-Ethanol

Amitriptyline has clinically important interactions with ethanol (Dorian et al., 1983). Five healthy volunteers received 25 mg of amitriptyline orally, preceded by 1 hour and followed for 8 hours by oral ethanol (or juice), doses adjusted to achieve and maintain blood ethanol concentrations of 800 mg/l. In the presence of ethanol, amitriptyline free plasma concentrations were increased by a logarithmic mean of 205 percent, 186 percent and 127 percent at 1.5, 2 and 2.5 hours, respectively, and amitriptyline free $AUC_{0\text{-}8h}$ was increased by 48 percent ± 13 percent (mean ± SEM) ($t = 5.21$, $p < 0.01$). Nortriptyline total $AUC_{0\text{-}8h}$ was increased by 26.6 percent ± 12 percent (mean ± SEM) ($t = 2.2\ 1$, $p < 0.09$). At the time of peak amitriptyline plasma concentrations, mean postural sway was increased over baseline by 92 percent with, and 2 percent without ethanol; likewise, mean short term memory (word recall) was decreased over baseline by 71 percent with, and 37 percent without, ethanol. Ethanol increases free amitriptyline plasma concentrations most dramatically during the period of drug absorption; this is due to a decrease in amitriptyline hepatic clearance, resulting in decreased first-pass extraction. Together with the pharmacodynamic interaction, the kinetic changes provide a rationale for the greater than expected toxicity of this combination and its deleterious effects on psychomotor skills.

Acute Ethanol-Zimelidine

Ethanol decreases the rate of biotransformation of zimelidine to norzimelidine by 46 percent, but the areas under the curve (AUCs) of zimelidine, norzimelidine, and their total concentration over 8 hours are not altered by ethanol (Naranjo et al., 1984a; Sellers and Naranjo 1988). Ethanol induced impairments in memory, body sway and a manual tracking task were further enhanced by zimelidine as was the ethanol induced decrease in friendliness. These potentiation effects include decreases in postural stability on one foot, recall memory, and "friendliness," but analysis of individual subjects shows that the effect of zimelidine with ethanol was often inconsistent in direction among subjects. By this

analysis, significant zimelidine-ethanol effects in a consistent direction include manual tracking and the "friendliness" rating. There were also inconsistent, but individually significant, results for the "sedation" rating scale. In this experiment, friendliness decreased further when zimelidine was combined with ethanol, indicating that zimelidinemodifies the effect of ethanol on mood and, therefore, that the drugs interact centrally. Since ethanol has positive and aversive effects, it is possible that zimelidine acts by modifying the balance of such effects, either by making the subjects perceive ethanol as less reinforcing, more aversive, or both, which might lead to decreased ethanol intake. However, we must be cautious in interpreting such mood effects since effects of ethanol on mood not only depend on dose but also on the psychophysiologic state of the subject and the context in which drinking occurs.

Chronic Fluoxetine, Amitriptyline and Ethanol

Several serotonin uptake inhibitors decrease alcohol consumption but not smoking and also decrease weight (Naranjo and Sellers 1988). Such effects may be mediated through effects on desire to drink and initiation of drinking (Naranjo and Sellers 1988; Sellers and Naranjo 1988). A study of chronic amitriptyline and fluoxetine and their interaction with ethanol has been conducted (Hamilton et al., 1987; Sellers and Naranjo 1988). Ethanol has no apparent effect on the pharmacokinetics of chronically administered fluoxetine or amitriptyline (Hamilton et al., 1987; Sellers and Naranjo 1988). The deleterious effects of ethanol on memory, manual tracking, body sway, intoxication and sedation were not modified by either fluoxetine or amitriptyline. Interestingly, chronic fluoxetine may have had some subtle effects on mood as reflected in the POMS (decreased friendliness) (Hamilton et al., 1987). Possibly such mood effects may be the reflectors of drug effects that correspond to the "urge to drink," "craving" or sense of "self-worth" or "need" for chemical reinforcement. Much further work is needed. If the initial observations are supported and extended they could serve as a basis for looking for generalization of drug abuse liability across patient populations.

NEW TREATMENT APPROACHES AND DRUG INTERACTIONS

Pharmacotherapy that could prevent or decrease the risk of drug abuse or could decrease non-therapeutic drug use would likely be widely accepted. Substitution therapy with nicotine-containing resin (Nicorette®) or with methadone for heroin abusers is well accepted despite evidence that the effects of drug alone are limited in size. Several additional therapeutic

approaches utilizing drug interactions deserve consideration, to decrease the probability of drug-taking behaviour or to decrease desire to use drug. Such approaches are properly considered drug interactions because prior drug abuse with its physiologic/neurochemical and behavioural consequences is required for the putative effect to occur.

Several possible interaction mechanisms need consideration:

1. Substitute a safer or kinetically more suitable drug or dose delivery form (e.g., nicotine patch, methadone maintenance).
2. Block the reinforcing effects of drug (e.g., naloxone, naltrexone).
3. Decrease the perceived effects of drug that reinforce behaviour.
4. Induce aversive reaction upon drug use (e.g., disulfiram).
5. Suppress target symptoms (e.g., anxiety, depression) which may prompt or sustain drug use.
6. Decrease the desire to initiate or continue drug use.
7. Cause non-specific side effects, e.g., nausea, which decrease the interest in consummatory behaviours.
8. Modify the kinetics of an abusable drug (e.g., slow absorption).

Formalization of the factors that motivate drug use appear in several theories (i.e., withdrawal model; compensatory model; opponent-process model). These have been recently reviewed and re-examined (Baker et al., 1988). The conclusions of this review are pertinenttoconceptualizing potential therapeutic strategies for use of drugs. Notwithstanding detailed differences in the major theories of why drugs are repeatedly or persistently used, all share in common (supported by much experimental, laboratory and clinical data) the idea that the desire to use drugs "reflects the presence of a drug-acquisitive motivational state." All three theories also involve the idea that desire for drugs is produced by drug-free related processes (cf., conditioned or physical withdrawal). Baker argues that urges may be elicited associatively (cf., directly) and non-associatively (cf., indirectly) by pharmacologic and non-pharmacologic cues that have motivational effects similar to unconditioned and conditioned agonist effects of drug. Baker further proposes that "urges" can be best viewed as affects (moods) with a wide qualitative and quantitative range. Fluctuations within the range can also occur. Such a view reconciles a large body of empirical clinical data and at least offers a framework for expecting identical behaviours (e.g., alcohol or drug consumption) triggered by positive and negative affects.

The searchforeffective drug treatments of alcoholism and alcohol-related problems centres on the potential value of serotonergic (5-HT) drugs. Recent reports of four clinical trials indicate that serotonin uptake inhibitors

(zimelidine, citalopram, viqualine, fluoxetine) decrease average alcohol consumption in humans by 10 to 20 percent (Naranjo et al., 1984b, 1987; Naranjo and Sellers 1988; Sellers and Naranjo 1988). These studies, conceptualized on the basis of the neurochemical modulation of consummatory behaviours, renew the hope that drugs may play an important role in substantial treatment progress in this field. Recent observations that 5-HT_3 antagonists can normalize drug withdrawal anxiety-like behaviour (Brittain et al., 1987; Costall et al., 1987, 1988; Kilpatrick et al., 1987; Jones et al., 1988) and decrease ethanol preference (Sellers et al., 1988) are important. In terms of the serotonin uptake inhibitors and 5-HT_3 antagonists, the incorporation of a careful consideration of the urges-affect-mood complex motivating drinking in drug abusers seems useful.

CONCLUSIONS

Since drug abuse has behavioural antecedents and consequences and rarely involves a single drug, a conceptualization incorporating drug interactions and multi-drug use is needed. Since abuse of a single drug is rare, drug interactions reflect the complex reality of drug use behaviour. The kinetic and dynamic aspects of drug interactions in abuse liability testing have been largely ignored. When more than one psychoactive drug is used, kinetic and dynamic interactions are inevitable. Apart from acute toxicity, the implications for behaviours such as risk to take drug and to stop using are rarely known. There is a reasonable probability that abuse liability can be decreased by other drugs and more effective discontinuation strategies developed.

1. The pharmacokinetic determinants of the abuse liability by individuals need much more study. The development of pharmacokinetic-pharmacodynamic models to better understand drug effects of abuse drugs should have high priority. Highly abused drugs (e.g., cocaine) are particularly useful but difficult to study model compounds. Such studies will require unique multi-disciplinary study teams.

2. The effects of prior and co-administration on abuse liability within a class of drugs and in some cases across classes are appropriate.

3. Detailed validated prior and current drug use including alcohol, caffeine and tobacco should be included in abuse liability studies. Agreement of a standard within the field could help.

4. More consideration should be given to how drug interactions could be used to therapeutic advantage:
   a) to decrease abuse liability and/or decrease the risk of toxicity; and
   b) to directly modify the desire to use a drug.

5. It is probable that interactions which decrease rate of drug absorption will lessen the probability a drug will be abused.

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CHAPTER 15

Promising New Biological and Behavioral Correlates of the Reinforcing Properties of Drugs

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INTRODUCTION

The pioneering studies of human drug abuse liability (Himmelsbach 1937a, b; Martin and Fraser 1961) involved volunteer participation by drug dependent men who were incarcerated in a federal penal institution. These volunteers also served as subjects in studies of biological and behavioral effects of abused substances for development of instruments such as the Addiction Research Center Inventory (ARCI)(Hill et al., 1963). The subjects who participated in this research were appropriately defined as "high risk" persons as a consequence of their drug abuse related problems prior to their incarceration. The logic of evaluating drug abuse liability for new compounds with such high risk persons is compelling, but it is unlikely that similar studies will be carried out in the future because of social, political and ethical concerns.

Subjects who participated in the original drug abuse related assessments carried out at the Addiction Research Center more often reported preference for a single drug than a history of polydrug abuse. In contrast polydrug abuse is highly prevalent among contemporary substance abusers and predictions about risk for polydrug abuse may not be generalized from studies of individuals who exhibit a single or a unique drug use preference. Moreover, we cannot assume that absence of a past history of substance abuse of any individual indicates lack of vulnerability for substance abuse problems for that individual in the future. There is now compelling evidence that a number of factors may predict occurrence of substance abuse problems long before the individual begins to use his or her substance of abuse. There is also increasing evidence that there may be a number of biologic markers which may be employed for

prediction of risk of substance abuse by individuals who have not, as yet, experienced any substance abuse problems. Although the discovery of biologic and behavioral factors which predict risk for substance abuse are probabilistic in nature and can rarely be used to identify a specific individual at risk, consideration of these factors may be important for the recruitment and selection of subjects who volunteer to participate in human drug testing paradigms.

SOCIAL AND BEHAVIORAL FACTORS WHICH MAY CO-VARY WITH RISK FOR SUBSTANCE ABUSE

Psychosocial and behavioral factors which may contribute to risk for substance abuse have been discussed by Nurco and by Kellam et al. in the 1981 Proceedings of Problems of Drug Dependence (Nurco 1982; Kellam et al., 1982). There is reasonably good evidence that antisocial and aggressive behavior are important predictors of substance abuse especially among males (Kellam et al., 1982). The relationship between shyness, aggressiveness, learning problems and substance use has been carefully delineated in longitudinal studies carried out by Kellam and his associates who found that:

> as early as first grade there are clearly identifiable antecedents leading to specific outcomes at least as far as 10 years in the future. Briefly, the findings are:
>
> 1. First-grade learning problems are the strongest predictor of teenage psychiatric symptoms for males. This effect is less clear for females. Learning problems do not predict substance use.
>
> 2. Among both females and males, higher scores on first-grade readiness and IQ tests in general lead to fewer psychiatric symptoms but more substance use 10 years later. However, the relationship of some symptoms to early cognitive performance appears to be more complex, showing a curvilinear relationship, with the level of teenage symptoms decreasing as one moves from the lowest to the average first-grade scores, but increasing with the highest scores.
>
> 3. Shyness among first-grade males (but not females) clearly inhibits substance use at age 16 or 17. For both males and

females, however, early shyness seems to predict higher levels of at least some teenage symptoms.

4. First-grade aggressiveness without shyness is a strong predictor of increased teenage substance use by males (not by females), but it is now associated with later psychopathology.

5. The combination of shyness and aggressiveness in first-grade males is associated with even more frequent use of substances (especially of cigarettes) than aggressiveness alone.

6. First-grade psychiatric symptoms as measured by both mothers' reports and clinicians' observations predict later symptoms for females but not for males.

7. With one seemingly minor exception, the SAS and PWB predictors do not interact in their effects on later substance use and pyschiatric symptoms.

8. The two outcome areas of psychiatric symptoms and substance use are empirically as well as conceptually distinct. They are barely correlated among male and female adolescents, and the developmental paths leading to them are very different.

9. There are strong differences between males and females in the developmental paths leading to adolescent outcomes. Early SAS has stronger predictive power for both later SAS and PWB among males (points 1,3,4 and 5), whereas early PWB shows continuity with later PWB only for females (point 6). The measures of cognitive achievement have similar effects for both sexes {point 2).

(Kellam et al., 1983, pp. 17-51)

Data obtained by Kellam and his associates suggest that substance abuse problems may have their genesis, in part, as a consequence of very early life stress and environmental factors. Assessment of these factors in a more systematic manner may provide a more rational basis for selection of subjects who participate in abuse liability assessments.

GENETIC FACTORS WHICH ENHANCE VULNERABILITY FOR ALCOHOL AND DRUG ABUSE

First-degree relatives of alcoholics are at greater risk for developing alcoholism than persons with negative family histories of alcoholism (Goodwin et al., 1973, 1974: Schuckit et al., 1972; Schuckit 1986; Cotton 1979; Bohman et al, 1981, for reviews see Cloninger et al., 1986; Russell et al., 1985). Although risk for alcohol and drug abuse involves an interaction of biologic, psychologic and sociocultural processes (for reviews see Mello 1980, 1983; Cloninger et al., 1986; Lex 1985), genetic predisposition is also probably a major risk factor for alcoholism .

Although it is clear that genetic predisposition cannot wholly explain risk for alcoholism (indeed genetic models can explain only a portion of the variance associated with the causation of most diseases) a number of biologic factors have been identified as putative genetic markers for enhanced risk for alcoholism. Among the most robust findings in this area are differences in subjective reports in levels of alcoholism-induced intoxication for persons with family histories of alcoholism in contrast to those who have no family history of alcoholism (Schuckit, 1984). There are also reports of differences in endocrine and neuroendocrine responses following alcohol consumption in family history negative and positive individuals, differences in derangements of psychomotor function induced by alcohol in family history negative and positive persons and differences in brain electrical activity during both basal conditions and in evoked response studies following alcohol intake by persons with negative and positive family histories of alcoholism (for review, see Schuckit, 1986). Taken together, data derived from biologic, psychologic and sociocultural studies suggest that, at least for alcohol abuse, individuals may possess differential vulnerabilities for development of alcohol abuse and dependence. Thus we may infer that a variety of biologic, behavioral and sociocultural factors may mitigate for or against many substance abuse problems. If this hypothesis is correct, it would appear reasonable to employ subject selection criteria for abuse liability studies which take into consideration relative risk as defined by biologic, psychologic and sociocultural predictors for substance abuse potential.

An excellent exposition of procedures available for testing drugs for physical dependence potential and abuse liability was published in a NIDA Research Monograph during 1984 (Brady and Lukas 1984). However, this report did not contain any recommendations for volunteer subject selection based upon biologic, behavioral or sociocultural antecedents as predictors of risk for abuse liability. The aim of this report is to discuss several promising new areas which may be of value in the conduct of abuse liability testing in the future. These studies involve

neuroendocrine, neurophysiologic and behavioral correlates of alcohol- and drug- induced intoxication, procedures for determining alcohol and drug effects on brain electrical activity with computer-based imaging studies and new technologies for assessing alcohol and drug concentrations in regional portions of the brain with Magnetic Resonance Spectroscopy.

NEUROENDOCRINE, NEUROPHYSIOLOGIC AND BEHAVIORAL CORRELATES OF ALCOHOL AND DRUG REINFORCEMENT

Covariance of neurophysiologic, neuroendocrine and behavioral events has been determined in human subjects during the first two hours after ingesting alcohol or alcohol placebo, administered under controlled double-blind conditions (Lukas and Mendelson 1988). Analysis of plasma adrenocorticotropic hormone (ACTH) and cortisol levels at 5 min intervals and EEG power spectral analysis in multiple 2-min epochs permitted examination of the biobehavioral correlates of intoxication. Data obtained establish that alcohol induces rapid changes in brain electrical activity and ACTH secretion from the pituitary that are correlated with subjective perceptions of positive changes in mood.

Methods

Twelve adult male volunteers ages 21 to 35 (57-98 kg) provided informed consent for participation in this study. Subjects were recruited via newspaper advertisements and were given a complete medical evaluation including an electrocardiogram, blood chemistry studies and urinalysis. Subjects with alcohol or drug abuse-related problems were not permitted to participate in the study. All subjects described themselves as social drinkers who, on the average, consumed alcohol one to three times/week.

Electrophysiological Recording and Blood Withdrawal Procedures

Subjects were studied while they were seated in a recliner chair, in a sound- and light-attenuated, electrically-shielded chamber, with their eyes closed (figure 1). Scalp electroencephalogram (EEG) electrodes were applied using the International 10-20 System (Jasper 1958) over sites C3, C4, P3, and P4. Electrodes were referenced to linked earlobes. A Kowarski-Cormed butterfly needle/catheter was inserted into an antecubital vein of the right arm and threaded through the chamber wall.

The end was attached to a syringe, mounted on a syringe pump and adjusted to continuously exfuse blood at a rate of 1.0 ml/min. Blood samples were collected at 5-min intervals to obtain integrative plasma levels of ACTH. cortisol and alcohol

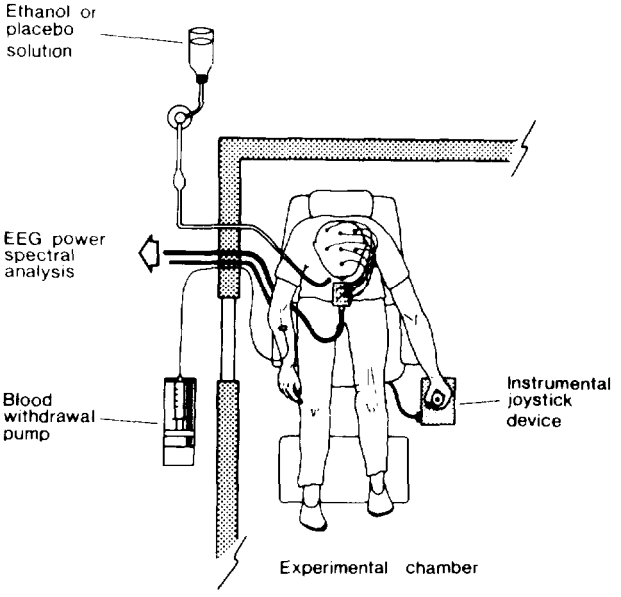

Figure 1: *Artist's rendering of a subject in the experimental chamber, demonstrating the multiple components of the study. Movement of the instrumental joystick device is recorded on the polvgraph, along with electroencephalographic activity. (Permission to reprint from Lukas and Mendelson 1988 from Biological Psychiatry.)*

Subjective Reports of Intoxication

Because verbal or written reports of perceived mood state changes may compromise the accuracy of EEG measures (Otto 1967; Matousek and Petersen 1983), a custom-made instrumental joystick device was used to obtain mood status reports. Movement of the handle or depression of the button resulted in a deflection of an event pen located on the polygraph. Thus, behavioral responses were monitored continuously with EEG activity. Details of the device are presented in Lukas et al. (1986a.b). These behavioral measures of mood status do not confound recording of electroencephalographic activity influence pituitary excretion of ACTH. Subjects were instructed to use their left hand to move the instrumental joystick device as follows: forward-when they detected an alcohol effect; left-when the effects became intense; backward-when the effects

disappeared. In addition, they were instructed to press a small button located on the top of the joystick during periods when they perceived feelings of intense pleasure, or euphoria.

Endocrine Assays

Consecutive 5-min integrated blood samples were subsequently analyzed for plasma ACTH, cortisol and alcohol levels. ACTH and cortisol were analyzed via radioimmunoassay procedures obtained from Nichols Institute Diagnostics, San Juan Capistrano, CA and Travenol Laboratories, Cambridge, MA, respectively. The ACTH assay is a double antibody procedure whereas the cortisol assay utilizes a single antibody procedure. Intra- and interassay coefficients of variance (CV) were 9.04 percent and 15.1 percent, respectively. for ACTH and 4.4 percent and 13.1 percent, respectively, for cortisol. Plasma alcohol levels were determined spectrophotometrically using the method of Leric et al. (1970). Intra- and interassay CVs were 3.0 percent and 7.4 percent, respectively.

Experimental Procedure

After 30 min of baseline recordings, subjects drank either a placebo or alcohol (0.695 g/kg) solution at a constant rate over a 15-min interval. A total of 350 ml was delivered via a drinking tube/peristaltic motor device which permitted the subjects to drink without opening their eyes or moving their hands. The placebo solution contained only grapefruit juice, whereas the alcohol solution was made with 40 percent beverage alcohol (vodka). For both doses a 10 ml reservoir located between the pump and the mouthpiece was filled with 3 ml of vodka to provide a strong initial taste to mask the two treatments. This practice is an effective placebo that does not produce measurable plasma alcohol levels (Mendelson et al., 1984). Electroencephalographic activity and behavioral responses were monitored continuously for the next 2 hours. Multiple 2-min epochs of EEG activity were subjected to power spectral analysis. Twelve-sev epochs were digitized at a rate of 256/set, followed by a Fast Fourier Transformation using a Pathfinder 11 signal processor (Nicolet Biomedical, Madison, WI). EEG power in the 0.25-4, 4-8. 8-13. and 13-30 Hz bands was determined and block averaged over 2-min intervals. Consecutive 5-min integrated plasma samples were removed without disturbing the subject for the duration of the study.

Results

After placebo administration, subjects did not report episodes of euphoria and there were no significant changes in plasma ACTH or cortisol levels or EEG alpha power. In contrast, after alcohol administration, subjects reported several paroxysmal episodes of euphoria which began within 10 min after drinking and continued for an additional 40 min. Plasma ethanol levels were 32.85 ± 5.35 mg/dl within 10 min after drinking began and peaked at 81.79 ± 5.35 mg/dl at 115 min after drinking. Plasma ACTH levels increased an average 20 pg/ml within 10-20 min after drinking began and subsequently declined. Plasma cortisol levels gradually increased and peaked at 30 min when blood alcohol levels averaged 44.98 ± 6.14 mg/dl.

Figure 2 shows regression lines for the linear portion of the time-effect curves for plasma ACTH, cortisol and alcohol levels, EEG alpha power, and the incidence of reported euphoria after placebo (top) and alcohol (bottom) administration.

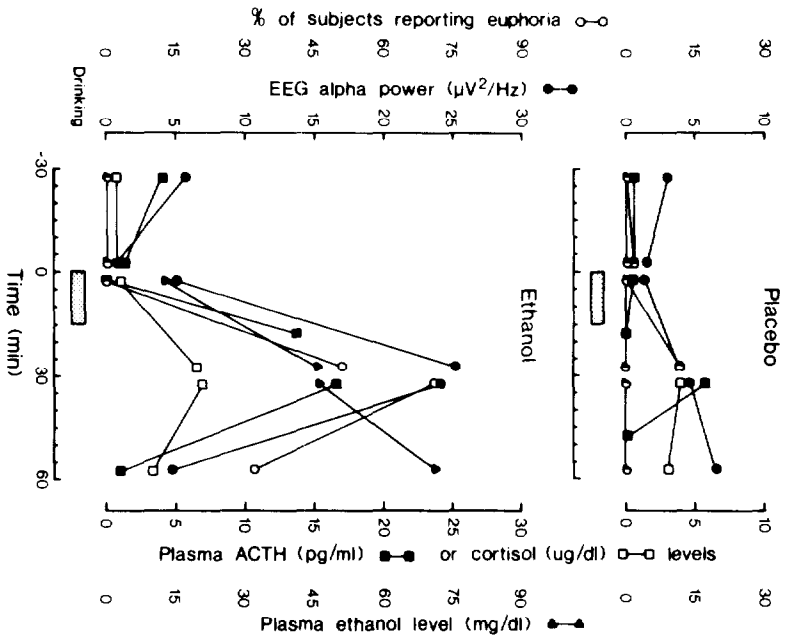

Figure 2: *Regression analysis of changes in plasma ACTH, cortisol. and ethanol levels, EEG alpha power, and incidence of reported euphoria after placebo (top) and ethanol (bottom) administration. Data are derived from six subjects per group. (Permission to reprint from Lukasand Mendelson 1988 from Biological Psychiatry.)*

Tests for parallelism (Tallarida and Murray 1981) revealed that EEG alpha power, subjective reports of euphoria, plasma ACTH levels, and plasma alcohol levels were parallel and all increased linearly during the first 30 min after alcohol consumption ($p < 0.05$). Increases in plasma cortisol were not statistically significant. All physiologic and behavioral measures decreased linearly within 35-60 min after drinking, even though plasma alcohol levels continued to increase.

Discussion

In the present study, subjective reports of self-perceived euphoriaoccurred between 10-15 min after drinking alcohol and were accompanied by a significant increase in EEG alpha power and increased plasma levels of ACTH. These data indicate that major physiologic and behavioral concomitants of alcohol intoxication occur at relatively low-blood alcohol levels (approx. 32 mg/dl) during the ascending phase of the blood alcohol curve. Previous studies have noted that alcohol intake is associated with activation of the hypothalamic-pituitary-adrenal axis (Mendelson and Stein 1966; Noth and Walter 1984), but we have been unable to locate any report that describes the initiation of such activation after such a short-time course and low blood alcohol levels following ethanol intake.

Enhanced secretion of ACTH at low-blood alcohol levels could be the result of alcohol-induced stimulation of corticotropin releasing factor (CRF). Although subsequent activation of the adrenal cortex following alcohol-related ACTH release could mediate changes in central nervous system function and behavior, ACTH and probably CRF itself may also directly effect neuronal function in regional portions of the central nervous system (Ehlers 1986). It is also possible that low doses of alcohol may directly stimulate release of ACTH from pituitary corticotrophs (Redei et al., 1986).

The acute effects of alcohol on human EEG activity consist of increased voltage and decreased alpha frequency (Engel and Rosenbaum 1945; Holmberg and Martens 1955; Varga and Nagy 1960; Docter et al., 1966). However, most of these studies have examined EEG effects that appear during the “peak” behavioral responses, which typically occur 30-75 min after drinking. Data obtained in this study and our previous study (Lukas et al., 1986c) focused on very early components of the alcohol response and found that neurophysiologic and neuroendocrine measures covaried with alcohol -induced intoxication in normal persons. Abrupt increases in EEG alpha power have been associated with specific subjective mood states generally reported as pleasurable, floating and extremely relaxed (Brown 1970; Lindsley 1952; Matejcek 1982; Wallace 1970). These data

suggest that the reinforcing properties of alcohol intoxication reflect these rapid changes in EEG activity and ACTH secretion. A previous study reported that acute oral administration of 40 mg of ACTH 4-9 analogue to human subjects reduced alpha activity (Bonn et al., 1984, 1985). However, this study was conducted to assess selective attention to a dichotic listening task which may have induced an alpha suppressing alerting response.

These positive early effects of alcohol are probably transient and dose-dependent, as high alcohol doses and chronic alcohol abuse are followed by increased anxiety, dysphoria and depression (Alterman et al., 1975; McGuire et al., 1966; Mello 1972; Melloand Mendelson 1978; Mendelson 1964, 1970; Nathan et al., 1970). Yet it is tempting to speculate that the early positive effects of alcohol may be especially salient for alcohol abusers. Alcohol abusers also have low amounts of spontaneous EEG alpha activity (Davis et al, 1941; Little and McAvoy 1952) and many abnormal endocrine and physiologic responses (e.g., impaired adrenocortical responses, regulation of arterial blood pressure) that are reversed or "normalized" after consumption of small amounts of alcohol (Kissin et al., 1959, 1960).

The paroxysmal short epochs of euphoria associated with concomitant neurophysiologic and neuroendocrine responses during the ascending phase of the blood alcohol curve may serve as powerful reinforcers for perpetuation of drinking. The rising phase of the blood alcohol curve may produce effects that are comparable to the heroin "rush" and cocaine "high" - intense sensations of intoxication that persist for seconds or minutes and then rapidly disappear.

Recent studies have shown that adrenocortical steroids may enhance or depress neuronal activity (Majewska et al., 1986) and that these changes may covary with positive and negative fluctuations in mood (Gold et al., 1986). Based on these observations, it has been postulated that adrenocortical activation of short-term duration which induces an acute glucocorticoid response may facilitate occurrence of positive mood states, whereas long-term adrenocortical activation and associated high levels of glucocorticoids may cause dysphoria (Barnes 1986). Data obtained in the present study are consistent with the notion that alcohol-induced ACTH secretion during the ascending phase of the blood ethanol curve covaries with subjective reports of euphoria and alterations of electrical activity in the central nervous system. Although chronic alcohol abuse, which isassociated with chronic adrenocortical activation, may increase risk for dysphoria, acute low dose alcohol intake clearly, induces euphoria. Thus the biphasic close-related effects of alcohol on mood may be mediated, in part, by the effects of alcohol on the hypothalamic-pituitary-adrenal axis.

TOPOGRAPHIC MAPPING OF EEG ALPHA ACTIVITY DURING ALCOHOL-INDUCED INTOXICATION

The same technologies employed in power spectral analysis, high-speed digital computers, are used to digitize the analog EEG activity, transform the data with a Fast Fourier Transformation (Walter 1963) and generate a power spectrum containing numerical values for the amount of power in specific frequency bands. Thus, quantification of brain electrical activity using power spectral analysis provides concomitant measures of power and frequency independent of sample length. Topographic mapping of brain electrical activity extends this technology because raw EEG recordings from 18 to 20 electrode sites contain more information than can be assimilated readily by the human brain (Duffy et al., 1979, 1981). Topographic mapping procedures assemble information from multiple EEG leads by simultaneously creating power spectral arrays from all electrode sites. The values between electrode sites are computed with a three- or four-point linear interpolation algorithm using the activity from the nearest three or four electrodes. The data are then combined into a composite color-coded (cf. Duffy et al., 1979, 1981) or gray-level (Buchsbaum et al., 1982) map which provides an overall view of brain electrical activity at the moment the map is generated. This technique has been used recently in the differential diagnosis of brain dysfunctions (John et al., 1988). Anextensivediscussionof the principles and the clinical and research applications of topographic mapping of brain electrical activity has been published recently (Duffy 1986).

Ethanol-induced changes in electroencephalographic (EEG) activity obtained using visual inspection and spectral analysis procedures include increased voltage and slowing of the predominant frequency (Davis et al., 1941; Abramson 1945; Engel and Rosenbaum 1945; Ekman et al., 1963, 1964; Docter et al., 1966; Begleiter and Platz 1972; Warren and Raynes 1972; Myrsten et al., 1975; Lukas et al., 1986a,c,d). While the results from these studies are fairly consistent, they were based on recordings from only a few EEG electrode sites, usually located over the occipital and parietal cortex. A re-examination of alcohol's effects on brain electrical activity has been prompted by recent technical advances in quantitative analysis of the topographic distribution of EEG activity using far more recording sites than previously employed.

Measures of brain electrical activity have been useful in characterizing various naturally-occurring behavioral states such as sleep and wakefulness, but EEG correlates of drug-induced euphoria, anxiety or dysphoria have been difficult to obtain. One major problem associated with determining the relationship between brain electrical activity and drug-induced mood changes is the procedural difficulty associated with

accurately measuring changes in subjective mood states without introducing EEG artifacts. The use of questionnaires and visual analog scales alters levels of alertness which, in turn, affect the EEG (Otto 1967; Matousek and Petersen 1983). Therefore, the use of a nonverbal instrumental device for recording drug-induced changes in mood is necessary to avoid disturbing the subject's level of alertness and thus altering EEG activity (cf. Lukas 1988; Lukas et al., 1986a,c).

Methods

Six healthy right-handed women (age 21-27 years, mean = 22.9; height 152-173 cm, mean=163.3; weight 54.3-79.1 kg, mean=64.7) volunteered for this study. Subjects were recruited via newspaper advertisements and were paid for their participation. After a full explanation of the nature of the study, all subjects provided informed consent for participation. All women received a complete physical examination including an electrocardiogram, blood chemistry and urinalysis evaluations. Beta subunit human chorionic gonadotropic hormone levels were measured l-2 days before the study to ensure that no woman was pregnant. Subjects with any neurological, psychiatric or alcohol- or drug abuse-related problems were excluded. Selection criteria also included a lean body mass of between 30 and 45 lbs/in to ensure minimal variability in ethanol volume of distribution (Reed 1978). Subjects were not currently taking any prescription medication, including oral contraceptives, and urine screens for recreational drugs were conducted on each study day-all results were negative. Analysis of the recruiting questionnaires revealed that all subjects described themselves as social drinkers who consumed, on average, the equivalent of 1-3 glasses of wine per week. All but one subject reported a negative family history for alcohol abuse or dependence based upon DSM-III criteria (APA 1980).

Experimental Design and Procedure

Each subject served as her own control and participated in the study on two occasions, 1 to 4 days apart (one subject was run 6 days apart) with the first study day occurring on the day after the last day of menses. Women were told that they might receive either placebo or alcohol on each study day. Each subject actually received alcohol on one day and ethanol placebo on the other in a randomized counterbalanced design. The alcohol drink contained 0.7 g/kg of beverage grade ethyl alcohol [86 proof vodka] mixed in chilled fresh orange juice. The placebo drink contained only orange juice. The total volume of both drinks was 350 ml.

To help mask the drink's content, a 10 ml reservoir within the straw was filled with 3 ml of vodka and 7 ml of orange juice to provide a strong initial alcohol taste before both placebo and active drinks were consumed (Mendelson et al., 1984). Subjects were informed of this procedure in order to discourage them from using taste as a discriminating cue. Both beverages were administered via a peristaltic pump located outside the experimental room (Lukas et al., 1986a,c,d) which delivered fluid at a rate of 23 ml/min to a mouthpiece. The mouthpiece was supported by a flexible metal arm to permit hands-free drinking and allow the subjects to keep their eyes closed and one hand on the joystick device (see figure 1) during the drinking procedure. The pump was activated for 3 min followed by a 1 min rest period. This procedure was repeated until the drink was consumed (19 min). Additional details of this procedure have been published recently (Lukas and Mendelson 1988).

Subjects arrived at the laboratory at 9:00 a.m. and reported that they had refrained from eating or drinking (except water) since midnight the night before. Fifteen to 20 min of baseline EEG activity were collected before alcohol or placebo administration. Since the major aim of the experiment was to study the early effects of alcohol , all measures were recorded for only 80 min after the drink was consumed.

EEG Recording Procedure

Subjects were prepared with 25 scalp electrodes affixed with collodion using the International 10-20 system (Jasper 1958). In addition, bilateral neck electrodes were attached to record muscle activity and two electrodes were placed above and below the left eye to monitor eye movements. Subjects were seated in a dimly lit room and the recording polygraph was located in an adjacent room. Unipolar activity from leads F3, F4, C3, C4, P3, P4, O1, O2, FPl, FP2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, Oz, linked eyes, left zygomatic, right zygomatic, and linked bilateral electrodes placed over the fifth cervical vertebrate were referenced to linked ear lobes and collected during eyes closed conditions using amplifiers at a bandpass of 1-300 Hz.

Topographic mapping of EEG activity was conducted using a Brain Electrical Activity Mapping(BEAM) system. EEG activity was recorded continuously during the study on a paper chart driver. Two to 3 min epochs of EEG activity were recorded on the BEAM system every 10 min forsubsequent power spectral analysis. Additional epochs were recorded during joystick responding.

Subjective State Assessments

Subjects reported changes in subjective mood states by moving the instrumental joystickdevice to indicate initial detection, strong intoxication and termination of alcohol effects (Lukas et al., 1986a,d). In addition, subjects could push a button to indicate an intense feeling of pleasure (euphoria); a second button was available to indicate an intense feeling of displeasure (dysphoria). Joystick movements were monitored continuously during the experiment and recorded directly on the paper chart driver, below the EEG recordings.

Blood Sample Collections

A standard i.v. flexible catheter was inserted into an antecubital vein. Patency was maintained by continuous saline drip which was connected via a 3-way stopcock. Discrete 5 ml blood samples were withdrawn at 10 min intervals for subsequent determinations of plasma alcohol levels. Blood samples were centrifuged immediately and the plasma samples were then frozen and stored for subsequent batch analysis for alcohol concentration. Parallel estimates of blood alcohol levels were obtained from a few subjects via expired air using a portable Alto-Sensor III device (Intoximeters, Inc., St. Louis, MO). Breath samples (obtained at the end of a 15 sec forced expiration) were measured once every 30-40 min and were gathered as part of a validation study to compare with measured plasma alcohol levels.

Data Analysis

Three 2-min topographic brain electrical activity maps were generated during the control period and at 10 min intervals after drinking began. EEG activity was not recorded during blood sampling or when subjects provided a breath sample. Additional samples of EEG activity were recorded when subjects pushed the button to report euphoria. Topographic maps of brain electrical activity were generated as follows. Digitized epochs of EEG activity were edited on a blind basis for eye and head movement artifact (abrupt deflections of 50 mV). Since the buttons on the joystick require only 1 Newton of force to operate, movement artifact was minimal or nonexistent: when present, only a 1-2 sec epoch of EEG activity required editing. Using the BEAM system software, Fast Fourier Transformations were perfomed on the remaining EEG activity. Brain electrical activity between electrode sites was calculated using a 3-point interpolation algorithm, and the resultant power spectral arrays were

color-coded on the basis of power in each of the following bands: delta (0.5-3.5 Hz), theta (4.0-7.5 Hz), slow alpha (7.5-9.5 Hz), fast alpha (9.5 12.5 Hz), $beta_1$ (12.0-15.5 Hz), $beta_2$ (16.0-19.5 Hz), and $beta_3$ (20.0-23.5 Hz). To avoid false interpretations due to truncation, the range of absolute values (μV) and corresponding color codes were used for data analysis, but then were scaled identically across all time points and subjects for graphic display.

Topographic maps were compared to a non-treated control database, consisting of thirty 20-29 year old right-handed women using significant probability mapping (SPM) techniques (Duffy et al., 1981). Significant probability mapping is a procedure that constructs z-scores for the voltage and frequency values at each data point. Brain electrical activity in each region of a subject's scalp is then displayed on a color scale that is calibrated in the number of standard deviations the subject's activity is from a control group. Because of the controversy surrounding the validity of techniques that employ multiple post hoc comparisons (Oken and Chiappa 1986; Duffy et al., 1986; Kahn et al, 1988), an alternative approach to quantifying the topographic maps was developed. This procedure involved collecting and storing the color-coded BEA-generated maps as gray scale images using a high-resolution digitizer/flat bed optical scanner and a microcomputer. The digitized images were then stored and loaded into a drafting program. The contours of individual colors on each BEAM-generated map were traced manually using a digitizing board and cross-hair puck, A yuantitative measure of the distribution of alpha activity over the scalp was obtained by determining the area (in mm2) of the various color-coded regions using the Show Area command of the graphics program (MacDraft). The area of each color was then multiplied by its corresponding voltage value provided by the absolute scale supplied with each topographic map; values for each voltage range were then added together to yield the total alpha energy of each topographic map. Additional details of this procedure are available from the authors.

Subjective report data were retrieved from the paper tracings as previously described (Lukas et al, 1986a,b,c). Mean latency to detection, intense intoxication and termination of alcohol effects as well as number and duration of euphoric and dysphoric episodes were determined after placebo and alcohol treatments.

Subjective Reactions to Alcohol and Placebo

All subjects discriminated correctly between alcohol and placebo; joystick responses indicating alcohol detection and intoxication reactions occurred

only after alcohol administration. Subjects detected alcohol effects (i.e., moved the joystick forward) within 15-25 min after drinking began. Alcohol-induced intoxication became more intense and was accompanied by multiple episodes of intense pleasure or euphoria (i.e., pushed button on joystick). Alcohol effects lasted 55.75 ± 20.1 min (range 30 - 79 min) in the five subjects without a family history of alcoholism. One subject detected alcohol effects for only about 15 min and failed to report a pleasurable response. Subsequent evaluation of this subject's history revealed that her father was diagnosed as alcohol dependent (DSM-III criteria). The temporal distribution of alcohol-induced subjective effects in subjects with a negative family history for alcoholism (FHN) and the one subject with a positive family history for alcoholism (FHP) are shown in table 1. While there was no difference in the latency to detection of ethanol effects, the FHP subject's response was markedly attenuated in both degree and duration. This differential behavioral response is depicted in figure 3.

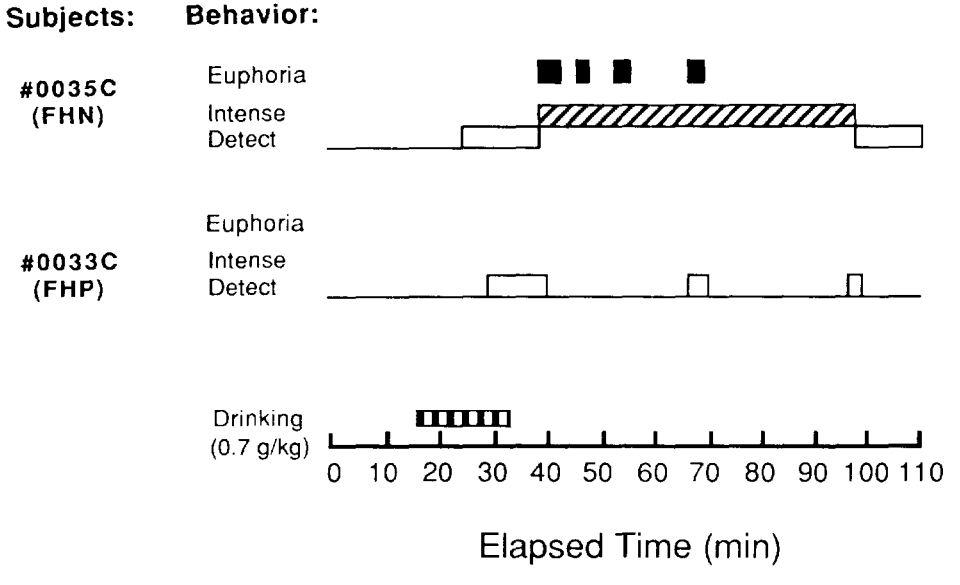

Figure 3: *Behavioral responses of a representative FHN woman and the on FHP woman after consuming 0.7 g/kg ethanol. Responses were recorded using an instrumental joystick device which was available continuously to the subjects throughout the duration of the study. (Reprinted from Lukas et al. 1989, copyright by Alcohol Research Documentation , Inc., Rutgers Center of Alcohol Studies, New Brunswick, NJ 08903.)*

Table 1. Latency to and duration of ethanol-induced intoxication in women with a negative (FHN) and positive (FHP) family history of alcoholisma

TREATMENT	LATENCY[b]			DURATION[b]	
GROUP	Detect	Intense	Euphoria	Detect	Euphoria
FHN (n=5)	19.60 ± 6.77	29.67 ±6.11	30.00 ± 6.08	55.75 ± 20.10	11.30 ± 17.30
FHP (n=1)	15.00	-------	------	15.50	-----

[a] 0.7 g/kg consumed over an 18 min interval.

[b] All values are in minutes (mean ± sem); latency data are from the onset of drinking.

Topographic maps of each frequency band (e.g.. delta, theta, alpha, beta) obtained during the pre-drink control period exhibited distribution patterns normally found during an eyes closed/quiet awake state (Gibbs and Gibbs 1951; Niedermeyer 1987). This included a localization of alpha activity over the occipital poles, midline theta and frontal delta. Ethanol-induced behavioral reports of intoxication were associated with alterations in brain electrical activity in the subjects with a negative family history for alcoholism. Figure 4 depicts this relationship for both a representative FHN subject and the one FHP subject.

In the FHN subjects, topographic mapping of alpha activity after ethanol revealed that the distribution of high-amplitude, slow- and fast-frequency alpha activity (white and red areas in the 4 right panels of figure 4) extended bilaterally to encompass parietal, temporal and frontal areas rostral of the central sulcus (electrodes C3-Cz-C4). Both slow and fast EEG alpha activity was reduced after ethanol in the FHP subject even though her plasma ethanol level (62 mg/dl via expired air analysis) was in the same range as the FHN subjects at the time these maps were generated. The results of the area analysis of alpha activity are shown in figure 5.

The overall ANOVA showed a significant effect of ethanol on EEG alpha activity $F(3.20) = 20.757$, $p < 0.001$. Scheffe F-test followup tests revealed significance ($p < 0.05$) after ethanol in both slow and fast alpha activity of the FHN subjects during the first 15 min after the drink was consumed while placebo did not significantly alter the topographic distribution of EEG alpha activity. The association between subjective reports of euphoria and increased alpha distribution was quite high ($r=0.61$, $p < 0.01$ for slow alpha and $r=0.74$, $p < 0.01$ for fast alpha); no subject reported euphoria at any time after receiving placebo. Slow alpha activity continued to remain elevated while fast alpha activity returned to control levels. The one FHP subject displayed a marginal decrease in both slow and fast alpha activity (figure 5), and reported only mild ethanol effects (see figure 3).

Significant probability mapping (SPM) techniques were applied to track the changes in alpha activity during the course of reported feelings of sobriety, intoxication and euphoria. Results from a representative FHN subject are shown in figure 6.

The color scale in a these topographic maps represents the difference between this subject and the subjects in the control database in units of standard deviations. The increased EEG alpha activity in frontal areas is evident by 30 min after ethanol at the time this subject reported an intense

pleasurable feeling. The last panel of this figure demonstrates that alpha power over frontal cortex has increased by 4 standard deviations (white area).

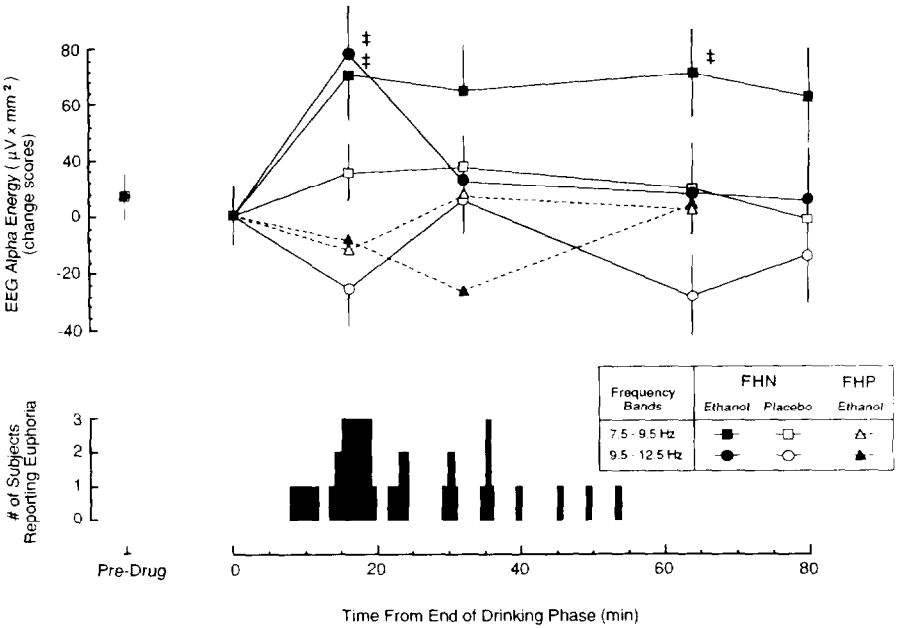

Figure 5: *Quantitative area analysis of slow and fast EEG alpha activity at various times before and after drinking ethanol (0.7 g/kg) or placebo in five FHN subjects and the one {dotted lines) FHP subject. The number and distribution of subjective reports of euphoria are plotted along the time axis for direct comparison. All five FHN subjects reported euphoria while the FHP subject did not. EEG alpha energy was quantified using a contour area analysis procedure. ‡ denotes significance atp < 0.05 level using ANOVA. Reprinted from Lukas et al. 1989, copyright by Alcohol Research Documentation, Inc., Rutgers Center of Alcohol Studies, New Brunswick, NJ 08903.)*

Plasma Alcohol Levels

All plasma samples from this study were lost due to a freezer malfunction. However, analysis of the occasional expired air samples revealed that subjects achieved plasma alcohol levels in the 70-80 mg/dl range. This was true for the one FHP subject as well. In another study from our laboratory, female subjects that received the same close of alcohol under the exact same conditions achieved similar plasma alcohol levels that peaked 60 min after alcohol administration.

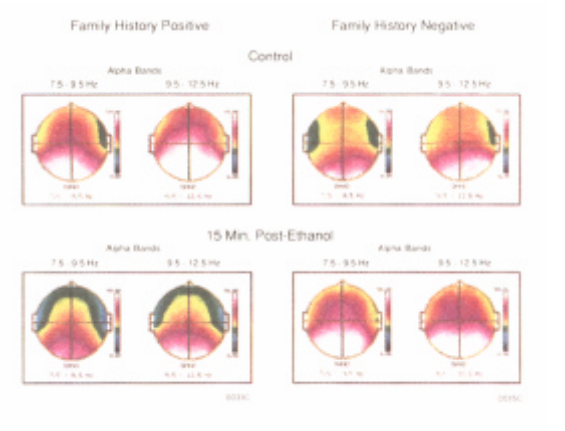

Figure 4: *Topographic maps of slow (7.5-9.5 Hz) and fast (0.5-12.5 Hz) alpha activity of the same two subjects depicted in figure 3. Maps were generated using a BEAM system during the control period and 15 min after the completion of drinking ethanol (0.7g/kg). Maps are plotted using identical scaling factors (0-50 uV) to aid in visual comparisons. Subjects' eyes were closed during data collection. (Reprinted from Lukas et al. 1989. copyright by Alcohol Research Documentation. Inc., Rutgers Center of Alcohol Studies. New Brunswick, NJ 08903.)*

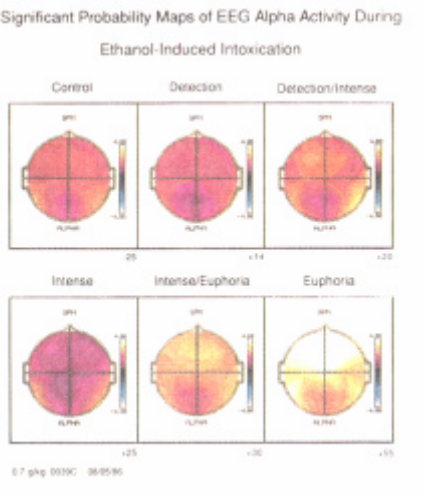

Figure 6: *Significant probability maps of EEG alpha activity from one FHN subject during the progression from a sober state to ethanol intoxication. Reference bars to the right of each map are calibrated in units of standard deviations of the control sample population (20-29 year old right-handed women) in the BEAM system database. (Reprinted from Lukas et al. 1989. copyright by Alcohol Research Documentation, Inc., Rutgers Center of Alcohol Studies, New Brunswick, NJ 08903.)*

Discussion: Topographic Distribution of EEG Alpha Activity After Alcohol

Alcohol-induced increases in alpha activity have been reported by a number of laboratories using selected scalp electrodes (Davis et al., 1941; Engel and Rosenbaum 1944; Newman 1959; Docter et al., 1966; Begleiter and Platz 1972; Lukas et al., 1986c,d). High-amplitude alpha activity is normally localized about the occipital area (e.g., electrode leads O1, O2, P3, and P4) and is usually most prominent when the eyes are closed. In the present study in which topographic mapping techniques were used to analyze EEG activity after alcohol administration, a unique pattern of increased alpha activity was found to encompass the entire scalp; this pattern was not observed during non-intoxicated states. While no left versus right hemispheric assymetries were observed, the recording montage (i.e., referenced to linked ears) was not suitable for detecting such differences. While low-amplitude, slow-frequency alpha activity can be recorded over the entire scalp, it is noteworthy that high-amplitude, fast frequency alpha activity is not normally recorded over the frontal cortex; this is the first report documenting an alcohol-induced alteration in the distribution of EEG alpha activity.

It is unlikely that the observed increases in EEG alpha activity are the result of neurophysiologic processes associated with intentional or voluntary movement (e.g., joystick responding). Control recordings obtained before drinking during simulated joystick responding failed to produce observable changes in EEG alpha activity. While voluntary movements can activate cortical recordings, particularly over the sensorimotor cortex, these effects are observed only when the movement is repetitive in nature and is paced over a specific time interval (Harner 1986; Pfurtscheller 1986). Joystick responding in the present study was limited to single movements of either the wrist or the index finger. Furthermore, voluntary movements reduce central beta activity (Jasper and Andrews 1938; Pfurtscheller 1981), and exogenous stimulation or increased attentiveness to the environment actually attenuates or "blocks" alpha activity (Morrell 1966).

Behavioral Correlates of Alcohol-Induced EEG Changes

All five women without a family history of alcoholism moved the joystick device to indicate that they were intoxicated. In addition. as observed in male subjects (Lukas et al,. 1986a,c), these women also reported that they experienced brief periods of intense pleasure or euphoria during alcohol intoxication. These subjective reports of alcohol

intoxication and euphoria were paralleled by abrupt increases in EEG alpha activity. Previous data from our laboratory (Lukas et al., 1986b) showed that reports of intense pleasure after marijuana smoking are also associated with abrupt increases in EEG alpha activity. Increased EEG alpha activity is normally associated with a pleasurable, free-floating and extremely relaxed state (Lindsley 1952; Brown 1970; Wallace 1970; Matejcek 1982) similar to that induced during transcendental meditation (Wallace 1970). The covariance between increased EEG alpha activity over the entire scalp and subjective reports of euphoria after ethanol suggests that this neurophysiologic response may be associated with ethanol's reinforcing properties. Hans Berger (1931) reported a similar increase in alpha activity after cocaine administration. Herning et al. (1985) replicated Dr. Berger's findings (i.e., a tendency for increased alpha) but noted that the lack of persistent alpha increases were due to the fact that the subjects in their study were required to perform a sequential subtraction task- thus, eliminating much baseline alpha activity. Therefore, it is plausible that increased EEG alpha activity may be associated with drug-induced reinforcement in general, and may not be selective for a single drug class. This interpretation is consistent with the notion that drug-seeking behavior is a form of stimulus self-administration that produces a change (regardless of the direction) in subjective state (Mello 1977, 1983).

EEG Indices of a Positive Family History of Alcoholism

The one woman who reported a positive family history of alcoholism experienced an attenuated behavioral and electrophysiological response to alcohol. Studies from other laboratories have demonstrated that subjects with a positive family history of alcoholism have a differential sensitivity to alcohol effects in comparison to subjects without this history. The observed differences have reflected almost exclusively an attenuated response in the FHP subjects as compared to FHN subjects. These include measures of body sway (Hegedus et al., 1984; Schuckit 1985), subjective reports of intoxication (Schuckit 1984; Pollock et al., 1986). motor control (O'Malley and Maisto 1985), spontaneous electromyographic activity (Schuckit et al., 1981). and spontaneous EEG; activity (Pollock et al,. 1983).

One laboratory that found a greater response in subjects with a family history of alcoholism reported that men with an alcoholic father exhibited alpha activity at a slower frequency than individuals without this history (Pollock et al., 1983). The effects of alcohol on alpha freqency have been shown to be dependent on the subject's baseline frequency (Engel and Rosenbaum 1945; Varga and Nagy 1960), and Propping et al., (1980)

demonstrated that alcohol elicited a more pronounced alpha rhythm in control subjects who have very little spontaneous EEG alpha activity. While it is likely that these variables could interact with the observed alcohol effect, the present results differ from those of Pollock et al. (1983) in that these investigators found that FHP individuals exhibited a greater increase in slow alpha energy and a greater decrease in fast alpha energy than FHN subjects after alcohol administration. In contrast, data from the present study indicate that a FHP subject exhibited less slow and fast alpha activity after alcohol. However, this subject exhibited more slow and fast alpha activity than the FHN subjects during control recordings (compare the top left panel with the top right panel of figure 2), so the direction and magnitude of the differences between FHP and FHN subjects may be less important than the fact that they differ from one another in their EEG responses to alcohol.

Additional evidence supporting a genetic component to alcohol's effects comes from studies in young boys who have a positive family history of alcoholism. Both spontaneous EEG activity (Gabrielli et al., 1982) and visual P300 evoked response potentials (Begleiter et al., 1984) differentiated these boys from control subjects without a family history of alcoholism. These data are particularly striking because these electrophysiological alterations were observed in the absence of alcohol administration. Similar data obtained in adults is not as conclusive since visual (O'Connor et al., 1987) but not auditory (Polich and Bloom 1986, 1987) P300 evoked potential amplitudes were lower in adult male subjects with a positive family history of alcoholism. Since spontaneous EEG activity is genetically related (Vogel 1970; Vogel et al., 1979; Propping et al., 1980), the data from the above and the present studies provide additional evidence that genetic predispositions to ethanol-related problems may be reflected in certain measures of brain electrical activity that are associated with the visual system such as visual evoked potentials and alpha activity.

Statistical Issues in the Analysis of Topographic Mapping Data

Abrupt increases in alpha activity were also observed using a statistical tool-significant probability mapping (SPM). Current limitations of the BEAM system prevent the creation of a separate database for the subjects in the present study, or for comparing individual subjects against one another, except by visual inspection. Thus, the SPM comparisons were made against a database. resident in the BEAM operating system, of 30 adult, right-handed females between the ages of 20 and 29. Recently. the validity of using significant probability mapping techniques as a diagnostic tool to classify a patient as either normal or possessing a specific disease

has been challenged (Oken and Chiappa 1986). Further, because of the complex nature of the data obtained, the collection process must be conducted with much greater care to ensure that the results are interpreted properly (Kahn et al., 1988). Duffy et al. (1986) defend SPM as exploratory in nature and emphasize that it is designed to localize regional differences in brain electrical activity, not for making diagnoses (Duffy 1982; Duffy et al., 1984). Oken and Chiappa (1986) argue that the use of "significant difference" tests for evaluating differences between control groups and patients must be based on planned comparisons between the control group and the patient. Since we were interested in analyzing only the distribution of EEG alpha activity after alcohol, the present study is not at variance with this notion.

One method of circutnventing this problem is to subject the topographic data to analyses that are especially appropriate for such graphic-oriented data--contour area analysis. The present study employed such a procedure based on digitized image reproduction using a microcomputer-based system. While it is clearly more desirable to use the actual data points generated by the BEAM system, these data are not easily obtained using the currently available software. Thus, area analysis of EEG topographic maps represents a compromise between the highprecisionof the algorithms in the BEAM program that generated the maps, and interpretable differences in area that yielded clear distinctions between treated and non-treated conditions as well as between FHP and FHN subjects.

Results from the present topographic EEG mapping study demonstrating that alpha activity was increased over the entire scalp and that these changes paralleled subjective reports of intoxication suggest that alcohol-induced increases in EEG alpha activity may correlate with its reinforcing properties. Previous reports from this laboratory (Lukas et al., 1986c; Lukas and Mendelson 1988) made a similar suggestion based on data from only a limited number of electrode sites; topographic mapping procedures used in the present study clearly provide a more detailed and descriptive analysis of this phenomenon. Since the alcohol-induced increases in EEG alpha activity were so widespread over the scalp, it is possible that this neurophysiological alteration may be related to processes which maintain continued alcohol-seeking behavior in spite of aversive consequences associated with its chronic use (McGuire et al., 1966; Alterman et al., 1975; Mello and Mendelson 1978: Mello 1983).

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY IN ALCOHOL AND DRUG ABUSE LIABILITY ASSESSMENT

During the past decade, major technologic advances have occurred in the use of nuclear magnetic resonance (NMR) spectroscopy for the non-invasive study of brain function. These studies require the use of specialized instrumentation which generates strong magnetic fields (current clinical instruments generate 1.5 Tesla, approximately ten thousand times stronger than the earth's magnetic sphere). However, strong magnetic fields, unlike ionizing radiation, do not produce any known safety hazard for human or animal tissues and organs. In order to determine the molecular structure of intrinsic oradministered compounds in the brain, induction coils connected to radio frequency oscillators and receivers are applied to regional portions of the head and neck. An NMR spectrum is generated by altering the strength of the magnetic field or the radio frequency; variation of the radio frequency signal permits identificationof variations of NMR frequencies of brain tissue components. Compounds which can be identified with NMR spectroscopy in the brain include those which contain the following atoms: ^{1}H ^{13}C ^{19}F, ^{23}Na, ^{31}P, ^{39}K. The natural abundance of all of these atoms exceeds 90 percent with the exception of ^{13}C which occurs in nature in approximately one percent of all carbon containing molecules.

Among the most important applications of NMR spectroscopy are *in vivo* studies of cerebral metabolic processes. These studies were pioneered by Ackerman and his associates (1980) and provided the basis for parametric determination of levels of high energy phospholated compounds in the brain by phosphorus NMR spectroscopy. Peres and his colleagues have utilized this procedure for studying effects of histotoxic hypoxia on intracellular brain pH and cerebral energy metabolism (Peres et al., 1988). More recently deterium oxide (2 H_2O) has been administered to determine *in vivo* blood flow and tissue profusion. The application of deterium oxide labeled compounds for studying drug distribution in regional portions of the intact human brain provides an exciting new opportunity for safe, non-invasive assessments of drug distribution and action in the central nervous system.

A major breakthrough in NMR spectroscopy has been reported very recently by Hanstock and his associates (1988). They have successfully measured alcohol concentrations in the human brain by proton magnetic resonance spectroscopy (Hanstock 1988). Following acquisition of a control spectrum, a subject consumed 750 ml of a beverage containing 12.5 percent alcohol. A second spectrum was obtained 50 minutes following alcohol intake, when blood alcohol levels were approximately

100 mg/dl(22 mM). At these blood alcohol levels, the brain concentration of ethanol methyl protons were approximately 60 mM. Dr. Hanstock and his associates concluded that "detection of a large ethanol resonance from the human brain is clearly practical. Since the ethanol protons are an AX2 spin system, the ethanol signal can be separated from coresonant signals by homonuclear editing if necessary. The way is open for systematic study of ethanol neuropharmacology directly in the organ of interest, with good time and anatomical resolution."

Incorporation of nuclear magnetic resonance spectroscopy studies in paradigms of human drug abuse liability testing will facilitate the discovery of biologic mechanisms underlying drug reinforcement. When such studies are complemented with improved psychologic and sociocultural assessments which predict risk for drug abuse, an exciting new area will have commenced for increasing our knowledge about abuse liability.

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CHAPTER 16

Drug Abuse Liability Testing: Human Subject Issues

Herbert D. Kleber, M.D.

INTRODUCTION

Clinical research, in general, is based on a tacit understanding between science and the larger society. Society is permitting certain risks to be taken with its members in return for the assurance by scientists that the research they are conducting is up to both scientific and ethical standards. Even if the ethics of a trial are justified, society is getting short changed if the science is inadequate. The results would not be able to be used for the benefits intended, and individuals would have been subjected to risks no longer justified by the benefits. The first scientific issue therefore has to do with whether a trial should be done at all (Marwick 1988). There needs to be adequate doubt about the outcome. For example, if one has a drug that structurally is similar to other drugs on the market known to be potentially abusable, and in animal tests of self-administration and other measures designed to measure human abuse liability, results are similar to these existing agents, one would need a very strong rationale to do human abuse liability testing. Unfortunately, animal testing not uncommonly is inadequte to the job of predicting human drug abuse. Certain drugs are self-administered by certain animal species and are not drugs of abuse in humans while, conversely, other drugs are abused by humans and are not self-administered by most animal species used in testing.

Once the necessity for a study is agreed upon, then the design of the trial becomes important. The design has to be such that the results are likely to be adequately conclusive. Too small an N to draw conclusions when a potentially dangerous drug is used is as unethical as an N larger than necessary for the study. Finally, there is the issue of obtaining an informed consent. Since, in general, self-administration studies are ones in which there will be no direct benefit to the subject, volunteers need to clearly understand this and the potential risks. The issue of compensation versus risk becomes important. It is also important, of course, to realize that the

assessment of risks involved in this kind of research requires certain assumptions or subjective judgments which are at times difficult to make and upon which reasonable people can disagree.

HISTORICAL BACKGROUND

The technological growth in research sophistication over the past 4 decades has been accompanied by increased understanding of important ethical dimensions, particularly regarding the use of human subjects. The low point in human experimentation was reached during the Nazi experiments in World War II. Revulsion at these atrocities led to the Nuremberg Code in 1946. Significant formal changes since then include: in 1953, the British Medical Research Council's memorandum on clinical investigations; in 1964, the Declaration of Helsinki; in 1966, the U.S. Public Health Service requirement for institutional review of experimental protocols involving humans; and in 1974, the establishment of a National Commission for Protection of Human Subjects of Biomedical and Behavioral Research. Just prior to this, in 1973, the Department of Health, Education and Welfare had published its first set of proposed regulations (these were finalized in 1974) on the protection of human research subjects. Between 1975 and 1978, the National Commission published a series of reports on various aspects of research involving human subjects. Each report presented recommendations to the Department of Health, Education and Welfare (DHEW) Secretary, recommendations which formed the basis of development of new DHEW and Department of Health and Human Services (DHHS) regulations. Commission recommendations have led to the DHHS regulations being far more rational than the original ones proposed in 1973-74. Since that time, Dr. Robert Levine, a staff member of the National Commission, has continued to be active in the field, and it is his writings in particular that have been of great help in formulating the discussion in this paper (Levine 1986).

FEDERAL GUIDELINES FOR RESEARCH ON HUMAN SUBJECTS

The DHHS guidelines for human research include the following points:

1. Risks to subjects are minimized proportionate to the anticipated benefits and knowledge.

2. Data are monitored to ensure safety of subjects.

3. Selection of subjects is equitable.

4. If subjects are vulnerable, additional safeguards are included.

5. Informed consent is obtained if appropriate.

6. Confidentiality is adequately protected.

The issues to be covered in this paper include the selection of subjects to be used, the relation of this to the type of drug, and informed consent issues.

ETHICAL PRINCIPLES USED IN DECISION MAKING

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1978) identified three basic principles of major importance in decision making in this area. They were: respect for persons, beneficence and justice. Respect for persons requires the investigator to treat subjects as autonomous individuals whose informed consent is necessary for participation in the research project. It follows from this that research subjects should not be considered passive data sources, but as individuals whose welfare and rights need to be respected. It is important to keep in mind that respect for persons includes the idea that if an individual is autonomous, he/she should be left alone to participate in activities even though such activities may be harmful, e.g., hang-gliding (Levine 1986). Individuals may be less than autonomous because of vulnerability, defined as being relatively or absolutely incapable of protecting their own interest. Vulnerability may occur because of insufficient power, intelligence, resources. strength, etc. The more vulnerable the individual, the less autonomous. The informed consent process needs to reflect safeguards with individuals who are deemed less autonomous and more vulnerable. As Levine has noted. “At times it is

essential to recruit vulnerable subjects because no other persons have the conditions to be studied. Under these circumstances one should generally select the least vulnerable representatives of those populations" (Levine 1986).

The second ethical principle is beneficence. Two general rules have been formulated as a complementary expression of a beneficent action including: 1) do no harm, and 2) maximize possible benefits and minimize possible harm. The Commission interpreted the principle of beneficence as creating an obligation to both secure the well-being of the individual and at the same time develop information that could lead to future societal benefit. It was important, they reported, to note, however, that securing societal benefits should not lead to intentional harming of subjects (National Commission 1978). While individuals taking part in research may be called upon to accept the risk of injury in the interest of producing a benefit for themselves or others, a researcher has the obligation not to take actions that would certainly injure an identified individual. The practical principles for researchers that flow from the principle of beneficence are as follows:

1. Protocols must provide valid and generalizable knowledge;

2. The benefits of the research need to be proportionate to the risks;

3. Since the benefits may be for others, subject well-being must be protected;

4. Researchers must try to minimize risk and maximize the benefits of participation;

5. Risks should be minimized by excluding subjects more likely to suffer adverse effects; and finally,

6. One way of maximizing benefits is to help subjects obtain care after the study has been completed if they are interested in treatment.

The third principle is that of justice. Justice is seen as requiring both that a person be treated fairly and that each gets what he/she is due or owed. Justice can either be comparative or non-comparative. Comparative is usually the case in research and involves determining what a person is due by weighing their claims against competing claims of others. Non-comparative justice deals with identifying what a person should do without regard to others, for example, that innocent persons should not be punished.

While comparative justice requires the fair sharing of burdens and benefits, what constitutes fair sharing is often a matter of controversy (Levine 1986). As applied to research the principles of justice can be stated as follows:

1. The benefits and burdens of research need to be distributed fairly.

2. No single group should bear a disproportionate share of the risk.

3. Vulnerable populations should not be used when other populations would be suitable study subjects.

4. Use of vulnerable subjects is more justifiable if the research will improve the understanding or treatment of the condition which makes the subjects vulnerable.

This last statement implies that, to the extent that drug abuse liability testing sheds light on those conditions which are predispositions or more likely to be associated with drug abuse and dependence, it is more justifiable to do such research with subjects who are vulnerable because they are already drug abusers. In order to determine what are appropriate groups for a particular research study, a researcher needs to identify those attributes that would permit adequate testing of the research hypothesis. As Levine has pointed out,

> In most biomedical and in some behavioral research, those attributes can and should be stated precisely in biological terms. In some behavioral and most social research, the attributes can and should be stated in social terms. An adequate statement of biological or social attributes that establishes eligibility for participation in a project includes criteria for exclusion as well as inclusion.
> *Levine 1986, p. 92.*

As a further corollary of this, one needs to consider what is meant by so-called normal controls or healthy volunteers. Levine again points out,

> It should be recognized there are no such persons. Normality and health are states of being that cannot be proved scientifically. Thus, such individuals should be described in scientific publications and research protocols as being free of certain attributes of non health or non normality.
> *Levine 1986, p. 93.*

For the research in question here, normal controls often means individuals who either are totally drug naive or who used drugs but did not exhibit compulsive or excessive use of such agents.

SELECTION OF SUBJECTS

Subjects to be used for human abuse liability testing can initially be divided into two groups: treatment seeking volunteers and non-treatment seeking volunteers. Treatment seeking refers to individuals in trouble with drugs and seeking help for such problems. In general, it would seem inappropriate in drug abuse liability testing to use treatment seekers unless such individuals would derive some direct benefit from their participation. Without that, the risk of prolonging the abuse or, even worse, having the individual change his/her mind about wanting treatment and go back to drug use would appear to outweigh the potential benefits to the larger society.

Left unanswered by this simple approach are two questions: Is it appropriate to use as subjects those seeking treatment for abuse of one category a drug of another category to test; and, is it ethical to use individuals who are seeking treatment but not for drug abuse, such as cancer patients who are seeking relief from pain. In regards to the first question, is it ethical to give a potential drug of abuse, say of the benzodiazepine group, to an individual seeking treatment for abuse of a morphine type drug or vice-versa? The underlying question here arises from the observation that there are major population differences between drug abusers and others in the liability to abuse certain drugs, raising implications for using that population in the testing. There are drugs that appear to have major addictive liability regardless of the psychologic or biologic characteristics of the population tested, and others that seem more limited in their appeal and are abused primarily by individuals who have already shown some propensity to abuse drugs.

A possible answer at this point might be that certain drugs, on the basis of their similarity to drugs with previously established high abuse liability and as a result of defined animal testing appear to be of high abuse liability, should not be given to any individuals seeking treatment. On the other hand, drugs with a predicted low abuse potential in relation to the above information might possibly be given individuals seeking treatment. Anexampleof this could be the use of a benzodiazepine in certain anxious opiate or stimulant addicts. Opiate addicts maintained on methadone are

well known to abuse certain benzodiazepines such as diazepam and lorazepam. However, they appear less likely to abuse oxazepam (Kleber 1986, DuPont 1988). Since anxiety is a common problem among opiate and cocaine abusers, a benzodiazepine that would be useful in treating anxiety in such patients and yet not be abused would appear to be of therapeutic benefit. It might thus be ethical to test such a drug on such treatment seeking patients.

In terms of the second question mentioned above, that is, whether individuals seeking treatment but not for drug abuse, such as cancer patients, should be used as subjects for abuse liability testing, again there might be situations in which they are potentially recruitable. If one has a potential new opiate, it might be reasonable to test in pain patients, to ask the question whether it would be self administered beyond the analgesic relief. Similarly, benzodiazepines need to be tested in patients seeking treatment for anxiety even though a certain percentage of them may abuse the drug. It would still appear ethical to test such drugs in these patients for abuse liability while recognizing the results would have limited generalizability.

One also has to be careful not to see drug abuse where it does not exist. I was involved recently in testimony before the Expert Committee on Drug Dependence of the World Health Organization (WHO) around the issue of whether clonidine should be scheduled. Clonidine, an alpha 2 adrenergic agonist has been used since 1978 to treat opiate withdrawal (Gold et al., 1978) and, more recently, to treat withdrawal from alcohol and nicotine. Unlike opiates which relieve opiate withdrawal by cross tolerance, clonidine appears to do it by its actions on the locus coereulus and noradrenergic activity. In general, clonidine does not have desirable psychic effects and there are less than a dozen cases reported of possible drug abuse (Schaut and Schnoll 1983), even though it has been given to millions of people in the decades it has been used to treat hypertension. However, because it was found in one country to be used by street opiate addicts, the assumption was made that it must be a drug of abuse. Overlooked was the more likely possibility that the drug was used to self medicate opiate withdrawal when narcotics were not available. As one who has tried to use clonidine for over 10 years in opiate withdrawal and much of the time has had difficulty getting patients to accept it, it was abundantly clear that clonidine is not a drug of abuse and fortunately the Expert Committee agreed with this assessment. The case points up, however, how easy it is to leap to certain conclusions from inadequate data bases and the importance of using a variety of indices to prove that a drug is one of abuse.

Historically, much of the early research on drug abuse liability testing in humans was done at the Addiction Research Center (ARC) at the Public Health Service Hospital in Lexington, Kentucky. The subjects were prisoners recruited from the prison population at the hospital who volunteered to take part in the various research projects at the ARC. Since they were prisoners, they probably would not be considered treatment seeking individuals, but on the other hand, given the restrictions on using prisoners for research study, it is likely that such research would not be permissible in today's climate. Prisoners are seen as vulnerable subjects because their consent may not be freely given (Levine 1986). Since they may not be truly free to refuse to participate and may be excessively influenced by considerations of money or early release, DHHS regulations restrict the type of permitted research. Lasagna has argued, however, that the work done at Lexington at the ARC is very difficult to do in alternative populations (Lasagna 1977).

One general reason for not using treatment seekers relates to the observation that today's drug abuser is more likely to be a polydrug user than an individual who sticks with one drug. However, even while using a variety of drugs there is usually one main or favorite drug for most of such patients. Our clinical experience with cocaine abusers, for example, suggests that one common reason for relapse when abstinent from cocaine for a period of time, is use of drugs that they were not previously addicted to, such as alcohol or marijuana, but which were often used in combination with cocaine. The feeling induced by these drugs serves as a conditioned cue leading the individual to crave the preferred drug while, at the same time, the altered state weakens the individual's ability to stay away from the preferred drug. Based on the work of Wikler and associates (Wikler and Pescor 1967) the conditioning laboratory at the University of Pennsylvania run by Dr. O'Brien and his associates has emphasized the role of conditioned cues in drug seeking behavior (O'Brien et al., 1986, Childress et al., 1988).

The next group of potential subjects are those recruited as volunteers, usually in return for monetary compensation. In theory, there are three sub-groups of individuals in the voluntary population among whom abuse liability might be quite different: individuals with a history of some form of drug abuse; individuals without such history, and also without any symptomatology that would require treatment by any of the drugs in consideration; and a third group that does have symptomatology such as anxiety, depression, pain or insomnia, for whom these drugs might be prescribed for clinical reasons. Since it appears that certain drugs may be more likely to be abused by individuals with an abuse history it would be

useful to include in the testing some such individuals. Individuals without such a history are necessary in order to obtain some estimate of whether the drug is likely to be abused by so called normals. Finally, one gains a very different kind of information by testing individuals who exhibit clinical symptoms. Some anxious individuals will not abuse benzodiazepines while others will.

Thus, among recruited volunteers there are two broad groups and sub-groups. The broad groups would be drug naive individuals and individuals with some history of drug abuse. For drug naive individuals, the question can be asked, is it ever appropriate to give a drug that the individual is naive to? There is no firm answer to the question. Some would argue that it is never ethical to give a drug to someone naive to that class of drug. Others would argue that the decision to use such individuals relates to the addictive liability of the class of drugs being studied. It may be more appropriate to use such individuals with drugs of predicted low abuse liability such as a benzodiazepine and much less appropriate for drugs of predicted high abuse liability such as stimulants. This begs the question of drug classes with intermediate liability such as analgesics and other sedatives. Although there are not as many epidemiologic studies as one would like on this subject, the few extant suggest that most individuals who try narcotic type drugs for non-medical purposes on a few occasions, do not go on to become addicted. The same is probably true for addicting sedative type drugs such as barbiturates. Likewise, the vast majority of individuals who take either of these two classes for a specific medical indication do not end up continuing their use after the medical indication has ceased. Thus, the answer for these two classes of drugs is less obvious than for the benzodiazepines, on the one hand, or stimulant drugs on the other. (There are also, of course, major variations within a class so that, for example, a stimulant such as caffeine may have less abuse liability than a member of another class).

Among drug users, again there are two general groups: users naive to a particular drug class being studied and users experienced with that particular drug class. One could further differentiate the class naive users into controlled users, who have used drugs but always in a controlled fashion, and individuals who have shown compulsive behavior to one or more classes of drugs but not to the particular class being studied. Among users experienced with a particular drug class, one has individuals with a history of control and those who have demonstrated compulsive addicted type behavior. Thus the question gets raised again - is it ever appropriate to give a drug class that an individual is naive to? If individuals are experienced in benzodiazepine use, can one ethically expose them to drugs such as stimulants and opiates or vice-versa. There appear to be,

among benzodiazepine users who become dependent on the drug, three categories. First, individuals who exhibit dependence on the drug at therapeutic dosage levels and who, although they have not escalated use, find it very difficult to stop the use even when their physician feels that they should. A second group of individuals are primarily multiple drug abusers with the benzodiazepines used as one among a variety of drugs. A third group of individuals abuse benzodiazepines at very high doses to achieve an intoxicated drunken state. Whereas existing data suggest individuals who abuse the benzodiazepine class are more likely to be individuals who have abused other drugs including alcohol, this appears to be less true among persons who became addicted to opiates. Many of them prior to exposure to opiates had not abused other drugs, although they may have used substances such as alcohol and marijuana. Although iatrogenic opiate addiction is not common, it occurs often enough that one recognizes it can happen to certain individuals. A substantial number of the soldiers at risk in the military zone during the Vietnam War became abusers of heroin. The subsequent cessation of such behavior for most when they left Vietnam suggests that the degrees of addictiveness of this class of drugs as with many other drug classes depends in part on the setting and the psychological state of the individual (Robins 1974). Stimulants are even further removed from the benzodiazepines and tend to have a relatively high abuse liability even in individuals who have shown no previous tendency toward drug abuse. Route of use, availability and setting, however, are factors here as well. Clinicians working with cocaine abusers often note their surprise that a particular patient has become a cocaine addict when there appears to be no significant psychopathology or prior drug abuse. Having said that, it is still important to keep in mind that the best predictor of cocaine use is heavy recent marijuana use. Among individuals who have used marijuana less than 10 times, use of cocaine is very unlikely. Among individuals who have used marijuana 100 times (e.g., averaged twice a week for a year), 75 percent of such individuals are likely to have at least tried cocaine and 15 percent will have used cocaine in the last month (Clayton 1985).

The problem therefore arises that it is not always possible to predict, from structure or animal studies, abuse liability, for example, whether a particular benzodiazepine is more like diazapam or oxazapam. While there are certain clues that one can obtain from pharmacokinetic data such as speed of onset, these may not always be reliable indicators. Therefore, one may be best off starting with experienced users or. even better. with abusers. If such persons like a drug and their behavior suggests they would abuse the drug if available, one still does not know whether non-abusing individuals would abuse it. Conversely, however, it is probably safe to surmise that, if persons with a drug abuse history do not abuse such a

drug, it is probably safe, for the most part, for persons without such a history. One should also keep in mind one might be thinking of heavy users rather than abusers in some circumstances.

From a regulatory point of view, if a drug is used and found "interesting" by abusers, should it be considered a drug of abuse or must it also be abused by naive subjects. As these data pile up, it will ultimately shed light on vulnerability to drug abuse in various population sub-groups and could be eventually used in prevention campaigns. Admittedly, of course, prediction even when related to class abuse liability is not infallable. Experienced clinicians have often encountered patients who are cocaine addicts who do not like opiates and, conversely, opiate addicts who do not like cocaine. Although there have been speculations about the self-medicating aspects of such drug choices and other rationales, we are still not very good at predicting the likelihood of any given individual becoming a cocaine addict or an opiate addict. This would suggest that it is important to test for drug abuse liability in individuals who are naive to that class of drugs even if they abuse other classes.

Thus a number of permutations and problems arise from the need to know whether certain drugs are attractive primarily to individuals with a drug abuse history as opposed to the larger population. Risk benefit ratios arise in such circumstances as manufacturers have to decide whether the purported advantages of a new drug outweigh its possible abuse liability. Even with very addicting drugs like cocaine, data from the 1985 National Household Survey suggest that for every eight individuals who try it, two continue to use it and one becomes a problem abuser or compulsive user. Thus roughly 25 percent of individuals who try cocaine continue to use it at least once a month and roughly half of these get into trouble with the drug. This is in contrast to alcohol, for example, where estimates suggest that of those individuals who continue to use alcohol after their first drug exposure, only about 10 to 15 percent get into trouble with the drug.

One needs a strong rationale for giving drugs of suspected serious abuse liability to either naive users or experienced abusers. There could be important therapeutic issues involved. For example, we could use an opiate with a better side effect profile. In order for the manufacturer to proceed with such an important compound, one would need animal data suggesting the better side effect profile and some efficacy testing even before testingforabuse liability. However. not too soon after, the liability testing should be done to avoid heavy development cost for a drug that ends up too addictive to be marketed. A new opiate with fewer side effects but more addictive liability would probably not be welcomed.

INFORMED CONSENT

Much has been written about the issue of informed consent and the most appropriate way to obtain it. This section will not explore all of the permutations but will primarily cover what is relevant for human drug abuse liability testing. For the consent of a subject to be valid, it must be legally competent, voluntary, informed, and comprehending or understanding. The relationship between the investigator and the subject differs from ordinary business transactions in which each party is responsible for informing themselves of the terms and implications of their agreement. Professionals who are acting upon the lives and health of others are held to a higher standard and are obliged to inform lay persons of the consequences of their mutual agreement (Levine 1986).

Creating a condition of informed consent involves both adequate informing, and paying attention to the process of consenting. The investigator needs to disclose information that will be relevant to the subject's decision whether or not to participate. Such information needs to include:

1. The nature of the research project;

2. The procedures of the study;

3. The potential risks and benefits;

4. Assurance that the participation is voluntary. (As a corollary of this, subjects need to know they can withdraw from the project at any time and that such declining to participate or withdrawing will not result in any penalty or loss of benefits);

5. Protection of confidentiality; and

6. The opportunity to ask questions.

Researchers need to be aware that the process of consent is more important than simply getting the subject's signature on a form. Brady noted in 1979, "a consent form does not informed consent make." He pointed out that the usual approach to informing is not the best design for getting the subject to understand in a meaningful fashion and suggested instead that, for complicated research activities, subjects would understand more if they were brought into the research environment and allowed to experience its routines and procedures (Brady 1979).

Human abuse liability testing raises certain issues relating to informed consent in the type of subjects often used. Consent, for example, may be invalidated by lack of comprehension such as produced by being under the influence of the drug. Persons under the influence may range from having very little trouble comprehending to having a total inability to comprehend. In other cases, the drug use may lead individuals to overestimate their capabilities and abilities to deal with the procedures. Informed consent, therefore, needs to be acquired when the individual is judged to be not intoxicated and able to comprehend the procedure (Levine 1986).

A second issue relates to what subjects should be told about the class of drugs to be studied. Should the exact class (e.g., stimulants) be divulged or only that the drug to be administered might be a stimulant, sedative, or inactive compound? The latter approach appears preferable in that sufficient information is being provided without compromising the research aim. How should the wording be done? Is the subject to be told, in essence, that the purpose is to measure abuse liability or only that he/she is being asked how much he/she likes or values the feeling of the drugs to be given. The latter approach again appears the preferable one but, under risks and benefits, the possibility that the drug could be one of abuse or dependence needs to be listed.

A third issue is confidentiality. Since some subjects will be individuals with a history of drug abuse or dependence, it is important that subjects be protected from the consequences that would occur if information about that were disclosed to employers, insurers, legal authorities, or even to significant others in the environment. Confidentiality may be breached if sensitive information is accidently disclosed, if the research records are subpoenaed, etc. Strategies that have been listed toprotectconfidentiality include storing the data in locked file cabinets, coding it to hide the identity of subjects, those having access to the research data destroying it after the study is completed, and insuring that individual subjects not be identified when the findings are published. Researchers also may obtain confidentiality certificates from DHHS and the Department of Justice which allows the identification of research subjects to be withheld even if the research records are subpoenaed. Potential threats to confidentiality as well as measures that investigators will take to protect it should be discussed explicitly with the subjects before they have to decide to participate. Researchers should be careful not to make promises about confidentiality that are impossible to uphold (Lo et al., 1988).

Institutional review boards are required under DHHS regulation to review proposed research to insure that it is ethically acceptable and that the welfare and rights of subjects are protected. It is important to keep in mind that the Institutional Review Board (IRB) system is not a central one; that is, each local IRB interprets and implements federal regulations using its own forms and guidelines. The IRB system does not insure that research is ethically acceptable. Individual boards may place emphasis on consent forms and on the risks and benefits of the research rather than on other ethical issues. Review of the scientific design which can be an important ethical issue, and of the approach in selecting subjects, is often left to the funding agencies and their external panels.

CONCLUSION

In the past three decades a number of drugs have been introduced into the marketplace as non-addicting but turned out otherwise. Meperidine, methaqualone, and pentazocine are the best known examples that come to mind. Although these drugs do not produce the major drug abuse problem of heroin or cocaine, concern in general over diversion of licit drugs to the illicit market and of iatrogenic addiction has led to enormous paperwork, detailed regulation, and physician underprescribing of needed analgesics. Earlier papers have shown that the knowledge base exists today for rational human drug abuse liability testing that can enable regulators, manufacturers, researchers, and physicians to have a much more scientific basis to predict potential abuse liability. This paper has laid out the human subject issues necessary to consider when doing such testing. Since animal testing remains imperfect for these purposes, it appears likely that human testing will remain necessary for a substantial period to come.

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CHAPTER 17

Issues in Human Drug Abuse Liability Testing: Overview and Prospects for the Future

Joseph V. Brady, Ph.D.

INTRODUCTION

The contents of this volume bear eloquent testimony to the great strides that have been taken over the past decade or more in the testing of drugs for abuse liability in humans. Less than 20 years ago there was virtually only one location in the world where the systematic study of drug dependence and abuse could be conducted with human subjects. The successors to those pioneers from the original Addiction Research Center (ARC) in Lexington, Kentucky who have contributed to this volume can point with pride to the roots from which this productive research technology has emerged. The early focus of these laboratories upon opioids clearly served to advance the basic scientific purpose of pharmacologically characterizing suchcompounds and facilitating development of safer and more effective therapeutic agents while reducing the risks of dependence and abuse. Most of the drugs upon which attention has continued to focus have well-defined current or potential clinical utility. Knowledge of their dependence potential and/or abuse liability is of obvious importance with respect to scheduling both within the United States and internationally. Under such circumstances, appropriate evaluation, to the extent that it is possible, prior to marketing is in everyone's best interest to avoid iatrogenic dependence and/or self-generated abuse as well as later scheduling after an expensive post-marketing experience.

We recognize, of course, that dependence and abuse are but some of the costs, along with other adverse side effects, that must be weighed against a drug's potential therapeutic efficacy. Ordinarily, a drug will not be tested for dependence potential and/or abuse liability until other aspects of efficacy and safety have been evaluated in a scientifically sound and systematic manner. It is of obvious importance then, that the assessment techniques that provide estimates of dependence and/or abuse risks meet the highest standards of validity and reliability. Such standards can be attained however, only when procedural foundations are conceptually and methodologically sound. Fundamental issues, in this respect, focus upon the identification, definition, and measurement of adverse effects in general, and drug abuse in particular, as manifest in the natural ecology.

In this latter regard, the interchangeable quasi-technical use of terms like "addiction," "dependence" and "abuse" as imprecise referents for a bewildering range of phenomena and experiential pseudo-phenomena continues to produce a degree of semantic and taxonomic confusion that is perpetuated in even the most current and authoritative treatments of the subject (e.g., Rinaldi et al., 1988; Johanson et al., 1987). The terms themselves, persistently reified as substantive noun "things" that enter into subject-predicate relationships with other "things" (and affect, as well as are in turn affected by these other "things"), are seldom accorded appropriate conceptual status as constructs emerging from observed relationships between specifiable antecedents (biological and social) and definable consequences (biochemical, physiological, and behavioral). Within this relational context, the analysis of interacting biological and behavioral events would seem to provide a basis for defining these constructs more operationally and specifying the conditions under which a unifying conceptual framework can be developed for this prominent aspect of drug use and misuse.

At least some definitional clarity has been attained by dividing the vast array of events that characterize this domain into two reasonably exclusive categories based upon explicitly operational criteria (Brady and Lukas 1984). Such a division is illustrated in figure 1, for example, by distinguishing between events that occur before and events that occur after actual substance intake. The defining operations of the "before" class, on the one hand, include proactive drug-seeking, drug-discrimination, and drug-taking behaviors. The defining operations of the "after" class, on the other hand, emphasize the reactive biochemical, physiological, and behavioral changes associated with tolerance and an abstinence syndrome when drug is withdrawn. Interactions between these proactive and reactive processes are of course, commonplace but their relative contributions vary with different pharmacological agents as a function of dose, environmental circumstances, and previous drug history (Mendelson and Mello 1982). Even more to the point of the topic to which this volume is addressed, the methods used to evaluate these distinguishable pharmacological actions are quite different.

The procedures described for human drug abuse liability testing in the present volume for example, share a clear focus upon proactive drug seeking and drug taking measures (i.e., reinforcing functions and self-administration performances). In addition, the treatment of self-report (i.e., "subjective effects") and drug discrimination measures emphasize their close conceptual and procedural ties. In contrast, little attention has been focused upon the reactive physiological-dependence measures that

characterize tolerance and withdrawal. The relevance and importance of this distinction between the proactive abuse liability and reactive dependence potential operations resides in the fact that from the perspective of drug abuse liability testing in humans - the topic to which this volume is addressed - their defining functions are not coextensive, they do not invariably occur together, and the methods by which they are evaluated differ. Proactive drug-seeking, drug discrimination, and drug self-administration performances as cardinal signs in the assessment of abuse liability for example, can be maintained in strength by use patterns and doses of compounds (e.g., cocaine) that produce no significant tolerance or withdrawal - the reactive changes traditionally associated with dependence potential. On the other hand, there are tolerance and abstinence-producing compounds (e.g., propranolol) that neither generate nor maintain drug self-administration.

It is important to emphasize that these distinctions between abuse liability and dependence potential are not merely academic since they bear directly upon the issues of validity and reliability. The methodological contributions described in the present volume document several converging lines of evidence - convergent operations, if you will - that

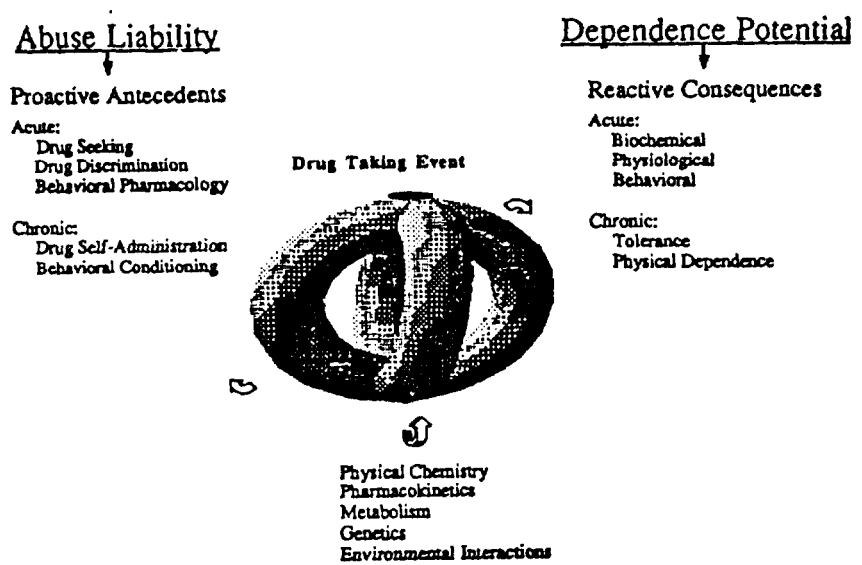

Figure 1: *Schematic characterization - Drug abuse liability and dependence processes.*

confirm the reliability and broad generality of observations relating the functions of drugs as both discriminative and reinforcing stimuli to the drug seeking and drug taking behaviors that define misuse and abuse. Moreover, the orderliness of the data relating these stimulus functions to independently derived measures of a drug's physicochemical properties and pharmacological activity (Griffiths et al., 1978; Brady et al., 1983), speaks directly to their construct validity in evaluating the contribution of such testing procedures for the assessment of abuse liability. But the issue of predictive validity on the other hand, has continued to plague even the most conscientious efforts precisely because it has been unclear as to just how drug abuse - the purported phenomena to be predicted - is to be appropriately identified, defined and measured in the natural ecology. Despite the persistence of differing opinions in these regards, operations that involve drug seeking, drug discrimination, and drug taking performances are clearly recognized as prominent and common features of the misuse and abuse process.

The point here of course, is that the validity of human testing procedures for assessing the stimulus functions of drugs are not to be judged on the basis of predicting "drug dependence" (i.e., tolerance and abstinence) nor even "drug abuse" (i.e., drug seeking and drug taking plus behavioral toxicity). Rather, their predictive validity resides in the evaluation of "abuse liability" (i.e., the likelihood that a given physiologically or behaviorally toxic substance will maintain drug seeking and drug taking under at least some conditions). An extensive array of biochemical substances have abuse liability under some conditions within the framework of this definition, and an evaluation of the stimulus functions of drugs provides information about at least these prominent aspects of the assessment process. To this extent, human drug abuse liability testing can be seen to have "face validity." Not only can it be determined whether there are at least some conditions under which a drug will be discriminated and self-administered (i.e., evidence of "inherent" reinforcing and discriminate functions), but to a significant extent, the range of those conditions can be defined (i.e., differences related to physicochemical structure, dose, time course, etc.) and the influence of circumstances (i.e., environmental contingencies, deprivation, etc.) in potentiating or attenuating such stimulus functions can be evaluated.

This broader environmental perspective of course, emphasizes not only the complexity of the etiologic and maintaining factors that characterize drug abuse but as well the web of social myths that surround the domain. These myths and expectations function in curious ways to exacerbate the problem by perpetuating notions and explanations that endow terms like "addiction," "loss of control" and "abstinence avoidance" with unde-

served explanatory powers (Levine 1978; Mello 1972; Maisto and Schefft 1977; Falk 1983). One advantage of the human testing situation should be its operational orientation which, though certainly not culture-free in any literal sense, does strive for definitional precision in clarifying the variables which institute and maintain drug abuse as well as the range of associated behavioral antecedents and biomedical consequences. Of particular interest in this regard for example, is the experimental evidence that the environmental context in which drug-taking occurs can dramatically alter the reinforcing function of even the most abusable substances. This contextual malleability of a drug's reinforcing efficacy has recently been documented with both cocaine (Spealman 1979) and nicotine (Goldberg and Spealman 1982) revealing that both drugs can have either pronounced reinforcing or punishing effects depending upon environmental contingency conditions. Such contextual malleability may well hold the key to at least some of the apparent inconsistencies in the results of human drug abuse liability testing. Furthermore, the results of recent laboratory studies suggest that excessive and chronic substance misuse and abuse may represent a set of behaviors for which others might have substituted (and intermittently do) rather than a highly specific disorder or disease state (Falk and Tang 1988; Vuchinich and Tucker 1988).

METHODOLOGICAL ISSUES

As a corollary of this contextual malleability of course, it must be recognized that there is a degree of inter-individual variability in reactivity to various chemical substances and that this reactivity can be modified by prior drug experience. This complicates the problem of insuring the validity and reliability of human drug abuse liability testing and requires not only assurances with regard to proximal drug free exposure in assessment settings but controls for drug-taking histories. Simple random assignment to drug and control groups is not likely to be sufficient in assuring the adequacy of an evaluation based on small samples. Care must be taken as well to insure the representatives of the population tested are distributed equally with respect to such obvious factors as age and gender. Likely attrition rates in human drug abuse liability studies that take weeks or months to complete (including follow-up) must be anticipated in screening volunteers and establishing incentive conditions. Important considerations relevant to endpoint analysis must be taken into account as well to avoid loss of data for those who do not complete the testing since those compliant with long and difficult studies are not always representative of the general population of potential absers.

ETHICAL ISSUES

In a volume so richly endowed with experienced and sophisticated author-investigators, these obligatory prescriptions must seem like so much "carrying coals to Newcastle." But in focusing on the human element in the drug abuse liability testing process, they do call attention to the ethical issues that must be confronted in evaluating the state of the art and science in this continuingly controversial domain (Brady 1979b). In keeping with my penchant for definitional priorities, let me first address the topic from the conceptual and methodological perspective that my card-carrying radical behavioral credentials require. Ethics would seem to be most parsimoniously viewed as a composite of values and morals. Values are the things people say are important to them - "justice," "liberty," "happiness" - and are for the most part abstractions. Morals, on the other hand, are the practices which the community rewards and punishes - "mother love," and "double parking." These foundations of our ethical standards are of course not immutable and can often be inobvious conflict - people have been known to say one thing and do another, in case you hadn't noticed! All of which is by way of acknowledging that we live in a consequentialist society and our standards, even our ethical standards, change as our practices bring us into contact with the environmental effects of those performances.

But the ethical issues raised by the use of human participants in testing the abuse liability of drugs are certainly not new or unique. Their roots can be traced at least as far back as the ancient controversies of vivisection and the more modem conflicts that have developed in the wake of the industrial revolution and the "fear of technology." And although technological transposition and public policy continue to provide the common thread which binds the problematic aspects of all human experimentation, it is of interest to consider why human drug abuse liability testing studies of the type so extensively treated in this volume are likely to attract special scrutiny.

There is one fundamental set of relationships which, if not unique to human drug abuse liability testing initiatives is at least displayed with "lightning rod" prominence in the "helping professions" at the forefront of these efforts. A basic concern in this regard focuses upon the so-called "boundary problem." Understated in obviously oversimplified form, it is not always crystal clear to either the patient-subject or doctor-researcher, much less to the spectator-public, just where the practice of the "helping professions" ends on the one hand, and the conduct of drug testing and orresearchbegins on the other. The difficulty in establishing this boundary arises largely because the setting, personnel, and maneuvers which characterize these interacting domains are frequently the same. Moreover,

human experimentation with its primary objective of generating new knowledge rather than helping a given individual was not differentiated conceptually before the 19th century. Until that time, it was embedded in the context of practice with no special ethical obligations formulated since the ethic governing practice (i.e., "no harm," "preserve life") was presumed sufficient for such experimental efforts generally viewed as attempts at patient benefit.

But the blurring of this boundary between research, testing, and practice can now be seen to have profound ethical significance, first and obviously because of the potential for conflicts of interest; and secondly because of the different ways in which uncertainty is to be viewed in the two enterprises. In the first instance, conflicts arise because the patient-subject who places himself in the hands of a practitioner-researcher does so primarily, if not exclusively, for personal benefit; whereas the doctor-investigator who accepts responsibility for invasion of the person commonly takes a much broader view of the benefits to be derived from the quest for new knowledge. At a minimum, under such circumstances there is the potential for a conflict of objectives, if not of methods and procedures. In the second instance, the conditions of uncertainty involved in the practice of a professional with a person presenting for direct individual treatment benefit are, by tradition, a private matter between doctor and patient with less stringent requirements for public scrutiny. On the other hand, the hypotheses and uncertainties associated with testing and the research quest for new knowledge - rather than direct individual benefit - clearly call for evaluation and validation by public assessment since the public is presumed to be the beneficiary of such new knowledge and must, for the most part, bear the burden (i.e., costs) of the research activity involved in its acquisition.

For all of these reasons, it has now become a matter of some import to be able to distinguish between drug testing research and medical practice since they are obviously under somewhat different contingency controls. Research and/or drug testing, for example, are clearly activities directed toward the development of or contribution to new or at least generalizable knowledge. They are characterized by explicit objectives and formal procedures designed to attain these objectives. Both are commonly set forth in a testing and/or research protocol.

This research and/or testing activity must be distinguished from the engagement in professional practice solely for the enhancement of an individual's well-being, with reasonable expectation of success as the standard. Indeed, the maintaining consequences of the "routine and accepted practice of" the helping professions have, by long and honored

tradition, focused exclusively upon patient benefit. There are, of course, instances where testing and/or research on the one hand and practice on the other, may coexist as is apparent from the contents of this volume (e.g., monitoring the effects and/or evaluating the effectiveness of treatment), but the aims and purposes, if not the methods and procedures, can, for the most part, be readily distinguished. Nonetheless, borderline areas do exist like innovative therapy, practice for the benefit of others, and nonvalidated practice. But the absence of precision or validation upon which to base an expectation of success in practice does not of itself define research and/or testing! Morally relevant concerns emerge on both sides of a dilemma posed by the potential for bad practice in the name of research on the one hand and research interference with treatment or service delivery on the other. There is obvious need, in the best interest of patient-subject and doctor-investigator alike, for clarification about which procedures are essential for treatment and which are introduced for research and testing purposes.

Among the more salient issues in this ethics domain is the so-called "risk/ benefit ratio." While it is clear that some balancing of costs and returns is necessary even in the domain of scientific testing investigations, the very use of terms "risk" and "benefit" to characterize these normative considerations in relationship to human drug abuse liability testing activities may be inappropriate at best and prejudicial at worst. An important advance is reflected in the emphasis upon "knowledge" as the product of such activity rather then "benefit" in the sense that the latter term is conventionally used in the context of professional practice. More importantly, the use of the term "risk," again carried over in large part from the practice context, creates the presumption that such effort should not be undertaken because of inherent "harms," and that these "harms" can only be outweighed by attendant "benefits," again conceptualized from the perspective of the individual "patient." Considered from a somewhat broader perspective, of course, all research and testing aims at certain valued returns or outcomes (e.g., increased knowledge, scientific understanding, helpful practical applications) and involves certain costs, including in some, but certainly not all, instances, possible harms (i.e., either individual or societal). The ethical task, in the face of these potential conflicts of obligation, simply said (but not so simply done!) is to insure an equitable balance between these costs and returns.

Such a characterization of the research and testing enterprise accords well, of course, with the basically "consequentialist" roots of normative ethical principles in Greek thought and Judeo-Christian tradition. But the conventional consequentialism of the practice ethic limits relevant consequences, for the most part, to the individual patient, and by

implication, limits experimentation and testing to that which is directly beneficial for that individual. This creates obvious problems for the moral justification of human drug abuse liability testing with such patient populations based upon the social value of the generalizable knowledge it produces. Indeed, the evident conflicts involved are clearly reflected in the traditional discomfort of patients and practitioners alike with such social value arguments in favor of research and/or testing participation when personal welfare considerations are of prime concern.

The moral force of these individual concerns notwithstanding, all of the recent codes which provide norms for the conduct and testing with human subjects (i.e., Nuremberg, Helsinki, The United States Department of Health Education and Welfare (DHEW), the American Psychological Association (APA)) subscribe in principal to a "bonum communum" defense of such initiatives. The countervailing influence to this "scientific rationalism" has been the rise of "western individualism" emphasizing self-determination as the basis of a political philosophy organized around the interpersonal contract. Perhaps the most significant consequence of this latter development has been the autonomous challenge to traditional paternalistic ethical norms that accepted, without question, "benefit" as a substitute for "consent." As a result, the right of individuals, as individuals, not to be "helped" is now being strongly defended.

Under such circumstances, it is hardly surprising that the "consent doctrine" has become the dominant ethical issue in research and testing with human subjects. The primary justification for requiring "informed consent," as distinct from a "consent form" (Brady 1979a), resides in the right of individuals to self-determine the use of their own persons, independently of any consideration of costs and returns. By implication, then, even cases which involve negligible or nonexistent costs would require consent to research participation. But what may not be so obvious is that this basic self-determination justification of the consent doctrine is a double-edged sword which also protects the right of an individual to participate in research which may not be cost-free or even harmless. In fact, considering these grounds alone, an argument can be made for limiting ethical oversight obligations to insuring the adequacy of consent procedures in the monitoring of research and drug testing activities.

Be this as it may, a second justification for the consent doctrine focuses upon protection of the person by insuring awareness of research objectives and procedures. At a minimum, this second justification preserves the right of research participants to make judgments in terms of the person's own values rather than proceed on the assumption that investigator's "advancement of knowledge" objectives are necessarily synonymous with "universal beneficence." It is the two qualifying descriptors, "free"

and "informed," then that are presumed to express distinctions between the self-determination and protection justifications of the consent doctrine. It is usually possible in practice to estimate the "degrees of freedom" in a choice situation by identifying alternative options. Infringements upon such "voluntarism" (a term preferable to "freedom" from a behavioral perspective) can be subtle in nature, however, and it is not morally sufficient merely to limit "force, fraud, deceit, duress, over-reaching, or other ulterior forms of constraint or coercion," as the extant codes and regulations require. True voluntariness depends upon the number of realistic options available *and* the extent of the individual's knowledge of these alternatives.

There is, of course, generally good agreement regarding the substantive nature of the information which should be made available to research and testing participants on the basis of a "reasonable person" (rather than a "fully informed") criterion. And no efforts have been spared to insure that investigators inform research testing volunteers with respect to the purposes, procedures, attendant discomforts, alternatives, and of course, their right to withdraw at any time without prejudice. The regulations and guidelines which have been promulgated in this regard provide for potent contingency management of the investigator's "informing" performances by negatively consequating even the faintest suggestion of compliance failure. But what of the human volunteers "knowing" or "comprehending" behaviors? With rare exceptions, no provisions appear to have been made for this "bottom-line" consideration in any of the ethical doctrines which have emerged in the human subject domain. What appears to be at issue is the "knowingness" of the subject and the evident difficulty in making determinations thereof based in-whole or in-part upon an evaluation of the investigator's informing behaviors. Even in those majority cases (hopefully!) where the subject can be presumed to have taken an active role in the information transfer, the formal characteristics of the procedure frequently suggest a heavy dependence upon "echoic" control (Skinner 1957) of the consent response. Parallels involving recitations of the "Lord's Prayer" or renditions of the "Star Spangled Banner": ("Oh say can you ..." consent) are not altogether facetious.

In contrast, of course, contingency management of the "knowing" features of the procedure would require performance evidence that the subject's consent repertoire is under consequential rather than antecedent control. Despite the hue and cry about additional burdens thus imposed upon the research enterprise, there do appear to be some investigative settings in which these basic requirements for "voluntary" and "knowing" consent can be approximated. At least one enlightened approach has been developed by Dr. Charles O'Brien at the Veterans Administration Hospital and University of Pennsylvania School of Medicine in Philadelphia.

Volunteers in Dr. O'Brien's drug testing programs are provided with instructional material and required to pass written and oral examinations on relevant experimental procedures, and the possible consequences thereof, before presentation of the consent formalities and participation in the research and/or drug testing are permitted.

These examples are obviously somewhat parochial and leave many difficult unanswered questions in research areas where the relevant knowledge of the informed subjects is less readily determined. But they do serve to emphasize the distinction between what is provided as information by the investigator and what is comprehended by the subject - more succinctly the distinction between "informed" and "knowing" consent. And lest these differences appear to fall in the realm of trivial semantic hair-splitting, consider the controversial subject-selection and special testing population problems with which this issue makes contact. Ethnic minorities and the poor, frequently with limited educational backgrounds, are very often the most likely volunteers for the human drug abuse liability testing programs which are the focus of this conference report.

FUTURE PROSPECTS

But so much for preaching to the converted. What of future prospects? It is obvious that explosive advances in new knowledgeof neurotransmitter and receptor dynamics will greatly enhance the development of effective therapeutic agents in areas that make direct contact with behavioral interactions and their subjective collaterals. It is equally obvious of course, that the very nature of such chemical interventions increases their vulnerability to misuse and abuse. By the same token, the potential for achieving unparalleled degrees of specificity in drug action afforded by sophisticated neurochemical analyses should make it possible to identify and parcel out desirable and undesirable features in characterizing the pharmacological activity of therapeutically promising agents. A critical element in this process will doubtless be the human assay methodologies that have been the focus of the contributions to this volume. The continued development and refinement of such human drug abuse liability testing procedures must keep pace with the pharmacological advances that will inevitably follow the progressive enlightenment produced by ever-expanding neural and behavioral science initiatives.

It might be argued in fact, that such human drug assay procedures should aspire to an even more prominent role in the advancement of safe and effective pharmacologic agents to the extent that their intimate contact with the behavioral repertoire of primary interest in this process - that of

the drug-taking human - makes them privy to effects and outcomes not always anticipated in pursuing the pharmacological equivalence approach to drug abuse liability testing. It seems reasonable to expect, for example, that the feedback from such human drug testing evaluations will enhance the process of drug development to the extent that valid and reliable behavioral changes can be identified and operationally defined in the productive give and take between the pharmacologists' bench and the clinical laboratory.

The final point to be made regarding the future prospects for human testing contributions to drug abuse liability assessment calls attention to one of the more complex issues in an already mind-boggling domain - that of polydrug use and the effects of drug combinations. The relative dearth of systematic research information in this area is of course a reflection of the rather primitive state of knowledge regarding drug interactions at the level of both the laboratory and the clinic. And yet it is in precisely this area where the human testing facility is likely to make a unique contribution to the evaluation of novel interaction effects. Certainly, the current lively interest in human drug abuse liability testing, generously reflected in the rich fare that graces this volume, more than guarantees the availability of a well-grounded foundation for the conceptual, methodological, and procedural advances that will berequired to meet these present and future challenges.

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CHAPTER 18

Conference Summary and Perspectives on Human Drug Abuse Liability Testing

November 5-6, 1988 - Scanticon Conference Center - Princeton, NJ

Mary Jeanne Kreek, M.D.

This two day conference, "Testing for Abuse Liability of Drugs in Humans," the culmination of an effort initiated by the Committee on Problems of Drug Dependence (CPDD), was planned, developed and brought to fruition by the enlightened, devoted, diligent and very talented efforts of Dr. Marian W. Fischman and Dr. Nancy Mello, current Co-Chairmen of the Human Testing Committee. This conference was appropriately co-sponsored by three United States Federal Agencies, the Drug Enforcement Agency (DEA), the Food and Drug Administration (FDA) and The National Institute on Drug Abuse (NIDA), all recognizing the need for further activity in this area of abuse liability assessment.

This meeting in part also reflected the earlier thoughtful contributions of the CPDD Human Testing Committee from the time that it was formed around five years ago and especially the efforts of its earlier Chairman, Dr. Charles O'Brien, and earlier Co-Chairman, Dr. Loretta Finnegan. The efforts of this relatively new Human Testing Committee were fully supported by my predecessor, Dr. Theodore Cicero, who was Chairman of the Executive Committee (now renamed the Board of Directors) of the CPDD, then by myself during my two, one-year terms as Chairman of the Executive Committee and Chairman of the, by then renamed, Board of Directors of the CPDD and especially during the current two, one-year terms of Dr. William Dewey, as Chairman of the Board of Directors of the Committee on Problems of Drug Dependence.

For many years, CPDD has sponsored and supported, in part, an active and highly respected pre-clinical program in abuse liability testing of new drugs under development, new chemicals which may be developed into new drugs, as well as sometimes already well-known compounds or approved drugs with newly suspected or recognized abuse liability potential. For many years this program was focused on testing of opiate

drugs and their congeners. In the last few years, an additional active program of testing of drugs in the stimulant and depressant classes as well as other related areas has been developed. As part of this program, many new testing procedures have been developed, others modified and all tests validated for use in abuse liability testing. Many different university as well as federal laboratories have participated in these efforts.

In recent years, it has become apparent to CPDD that abuse liability testing of new drugs in humans which was already being carried out, but to a limited extent only, in several governmental and academic laboratories, is an extremely important endeavor, one for which many new techniques have been developed recently, or are being developed and for which old techniques have been further refined in recent years. It was also recognized by CPDD that abuse liability testing in humans is an effort which logically should be nurtured by CPDD and coordinated under the broader Drug Testing Program which has up to this time carried out both chemical and *in vitro* laboratory procedures as part of its effort, in addition to the very well developed multi-center Animal Testing Program.

Therefore, the Clinical Testing Committee of CPDD was formed and given the mandate to determine what role CPDD could and should play in this area of urgent need. It was soon recognized that, in the tradition of CPDD, coordination of a scientific meeting designed to bring together both experts in this area and those in potential need for use of the techniques of abuse liability testing in humans, including appropriate persons from academic, governmental and corporate sectors, was needed. The Board of Directors of CPDD agreed that holding such a conference was a high priority need. The result has been this meeting.

During the two days of this conference, superb presentations were made by speakers from the United States and from abroad. The meeting was very informative throughout, both in the state-of-the-art scientific presentations providing specific information about human testing procedures, and also the didactic lectures on current mandatory procedures and desirable future procedures with respect to regulatory issues which must be addressed with respect to drug abuse liability testing in humans. The conference also included many lively discussions on public policy issues, federal and corporate perspectives on this topic and the ethics of human research in this challenging area of drug abuse liability testing. Many of these presentations and discussions are to be included in the forthcoming NIDA monograph resulting from this conference.

However, in summarizing this conference, it is clear that certain very important questions remain to be answered. Also the future role that

CPDD should play in this effort of abuse liability testing in humans remains to be defined. Some of the more difficult, yet pressing questions to be answered include the following:

(1) Which drugs, or classes of drugs, should be evaluated for abuse liability?

- Drugs related chemically or by pharmacodynamic actions to drugs known to have an abuse potential or which are already abused or used non-medically?
- All drugs in the psychotropic drug classes?
- All drugs known to affect learning and memory?
- All drugs known to have some direct effects, either a primary effect or a side effect on the central nervous system?
- All drugs known to have a primary or secondary direct or indirect effect on the central nervous system?

(2) Who should make the decision as to whether a specific drug or a class of drugs should undergo abuse liability testing in humans?

- The Federal Government (FDA, DEA, other agencies)?
- The corporate sector (a single company developing the drug; a coalition of companies within an umbrella organization, e.g. the Pharmaceutical Manufacturers Association)?
- The academic sector?
- Consumer groups or other groups of lay persons?

(3) How is the decision with respect to whether or not any given drug or class of drugs is to be tested to be reached?

- Is a decision to be made to determine whether it is desirable, essential, or in fact mandatory that a specific drug be tested?
- What group or groups should confer in the decision to suggest or demand that a specific drug undergo such abuse liability testing in humans and also decide how and where such testing should be performed and which tests should be performed?
- What kind of expertise is needed to reach a decision that balances on one hand what is desirable, essential, or mandatory, with the recognition of limitations of existing

resources for such abuse liability testing in humans, including limitations of funds and skilled staff to expand existing resources or to develop new ones?
- What group or groups should resolve the issues of relative cost compared with the relative benefit of such abuse liability testing in humans for a specific agent?

(4) When in the course of new drug development should such abuse liability testing in humans be performed?

- As part of Phase I, that is, the first introduction of the drug into humans?
- As part of Phase II, the first use of drugs for the target condition in patients with the disorder under study?
- During Phase III, when wide-scale clinical trials of the drug are being carried out in target populations?
- During Phase IV, after large scale clinical trials have been completed and frequently a New Drug Application has been approved, as part of post-marketing surveillance?
- After identification of actual abuse or non-medical use of the agent has been made by epidemiological or post-marketing surveillance studies?

(5) What kinds of specific tests for drug abuse liability assessment in humans should be performed and by whom?

- Should drug discrimination testing be performed?
- Should testing for reinforcement properties of the drug be performed?
- Should other related or unrelated indices which may indicate abuse liability potential, such as testing of the effects of the drug on neuroendocrine or on neurotransmitter systems, be performed?
- By what means will sites be identified and recognized, within the academic, governmental and commercial sectors, where validated testing procedures are ongoing and where clinical research or evaluation workers skilled in carrying out such procedures are available, or alternatively, where testing procedures developed elsewhere could be set up and validated and staff could be trained for carrying out such procedures?

(6) Who should be tested, that is what kinds of volunteer subjects should undergo the experimental testing for abuse liability of drugs?

- Any normal volunteer subject?
- Volunteer subjects with a history of substance abuse or addiction of any kind?
- Volunteer subjects with a history of substance abuse or addiction involving compounds similar to the drug to be studied?
- Volunteer patient subjects with the condition for which the drug is to be targeted in appropriate therapeutics?

(7) By what mechanisms can ongoing surveillance for appropriate use of therapeutic agents, as contrasted with inappropriate or non-medical use of such agents, or even illicit trafficking, misuse, abuse, and possibly addiction to such agents, be identified, both before and following any FDA New Drug Approval, given the constraints of confidentiality and the complexities of the health care system which currently exist in a country like the United States?

These are some of the more important issues raised during the conference, some of which were partially addressed during the conference and its open discussions, though none were fully answered. Many of these questions as well as other related issues are crucial for the further development and application of procedures for abuse liability testing of drugs in humans.

Finally, the question of what should be the continuing role of the Committee on Problems of Drug Dependence, in view of its very long 60 year history of scientific inquiry and communications in areas related to drug abuse and dependence liability as well as its almost equally long history of preclinical abuse liability testing. Certainly as evidenced by this conference, CPDD has ample expertise within its members and its colleagues to reach out to both the scientific community and the policy making community to address issues related to this topic. CPDD also has the enthusiasm about the topic and insights into the ramifications of such testing as well as a commitment to the concept of need for further abuse liability testing in humans at this time. However, decisions still will have to be made as to what is the most appropriate, acceptable and feasible role of the Committee on Problems of Drug Dependence in testing for abuse liability in humans in the future.

All of us who are members of CPDD as well as others who attended and hopefully benefitted from this meeting, wish to express our special gratitude to Drs. Fischman and Mello for their tireless efforts in the development and presentation of this conference. All of us from CPDD would also like to thank our colleagues in the federal agencies which co-sponsored this meeting, DEA, FDA and NIDA for their help and support. Finally, we would like to thank all of those who attended and actively participated in this conference, from the academic, corporate and public policy sectors.

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