National Institute on Drug Abuse

Research 55

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Problems of Drug Dependence 1984

Proceedings of the 46th Annual Scientific Meeting

The Committee on Problems of Drug Dependence, Inc.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

Problems of Drug Dependence, 1984

Proceedings of the 46th Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc.

Editor: Louis S. Harris, Ph.D.

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Foreword

The National Institute on Drug Abuse presents once again to readers of its Research Monograph series the Proceedings of the Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc. NIDA and the CPDD share many interests and concerns in developing knowledge that eventually will lessen the destructive effects of dependence-producing substances on individual lives and their costly burden on our society as a whole. As would be expected, the two organizations work closely together.

CPDD's Annual Scientific Meetings gather the outstanding investigators from many disciplines to discuss their ongoing projects. Researchers from NIDA's own Addiction Research Center report their findings here. In addition, the work of many other CPDD members and meeting participants receives support through NIDA's grant programs. The CPDD drug testing program to assess the dependence potential and abuse liability of new compounds is also NIDA-supported. Results of these tests, which seek analgesic drugs free of abuse hazard, are included in each year's Proceedings.

A symposium on the neuroendocrine effects of substance abuse is featured in Problems of Drug Dependence, 1984, in addition to papers on chemistry and pharmacology, clinical pharmacology, treatment, and epidemiology. It is gratifying to make available to drug abuse professionals and to the public this yearbook of current research on all aspects of the drug abuse field.

William Pollin, M.D.
Director
National Institute on Drug Abuse

The papers in this monograph were presented or read by title at the 46th Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc., in St. Louis, Missouri, June 4-6, 1984. The CPDD, an independent, nonprofit organization, conducts drug testing and evaluations for academic institutions, government, and industry. Louis S. Harris, the editor of the monograph, is chairman of the Department of Pharmacology, Medical College of Virginia, Richmond, Virginia.

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Presentation to Kay Croker of J. Michael Morrison Award for Outstanding Achievement in Science Administration in the Drug Field

Martin W. Adler

Michael Morrison was an exceptional young man who embodied all those qualities one hopes to find in an administrator. When he died about four years ago at the age of 36, Mike was Executive Secretary of the Biomedical Research Review Committee at the National Institute on Drug Abuse. Upon his death, his friends and colleagues felt that the most appropriate memorial would be an award honoring outstanding achievement as an administrator in the drug field. The Committee on Problems of Drug Dependence, Inc., agreed to administer the award and present it biennially. This is the second such award.

Our awardee embraces all those qualities we so admired in Mike. She is warm, dedicated, hard-working and extremely knowledgeable in all areas of her work. Kay Croker has been with the American Society for Pharmacology and Experimental Therapeutics since 1977, rising from the position of Editorial Assistant to Administrative Secretary for the Executive Officer in 1982. To give you some idea of what the members of ASPET think of Kay, at the last business meeting of that society just two months ago, the report of virtually every committee was followed by that chairperson's singling out our awardee for special thanks for the way she aided the committee in achieving its goals. All it seems to take are workdays that often extend 14 to 16 hours, a flair for organization, a love for her job, and a warmth that makes everyone comfortable.

For her outstanding achievements as as administrator, I am very pleased and honored to present the J. Michael Morrison Award for 1984 to Ms. Kay Croker.

Introduction of Nathan B. Eddy Memorial Award Recipient—1984

Louis S. Harris

It gives me great personal pleasure to introduce this year's recipient of The Nathan B. Eddy Award. Dr. Raymond Wilfred Houde was born in New Hampshire and educated in New York, receiving both his Baccaluareate and Medical degrees from New York University. After a brief internship at Bellevue, he was on active duty with the Navy from 1944-46.

He completed his residency in medicine at Memorial Hospital, a connection he maintained until his retirement in 1982. From 1948-50, he was a Research Fellow in Analgesia at Memorial Hospital and Sloan-Kettering Institute. He used this time to spend a year first in the Pharmacology Department at The University of Michigan and then at the U.S. Public Health Service Hospital in Lexington, Kentucky.

At Michigan, with Sam Irwin, a graduate student at that time, he studied the effects of narcotics on reflex responses to nociceptive stimuli in spinal animals. This interest was further pursued with Abe Wikler at Lexington. It is noteworthy that Dr. Houde was the senior author on the first paper delineating the usefulness of the chronic spinal dog in evaluating analgesic and other centrally acting drugs.

Following this training, Dr. Houde continued his uninterrupted career at Cornell University Medical School and Sloan-Kettering, rising through the ranks in both the Departments of Pharmacology and Medicine with the encouragement of NBE. His research became more clinical and he developed his first-rate team of Stan Wallenstein and Ada Rogers, who have remained together to the present. Indeed, in his pioneering use of a nurse observer, etc., not only did this team turn out some of the best clinical research in the area of pain and analgesia, but they trained a host of clinical pharmacologists, many of whom have gone on to highly productive careers of their own. These include, to name a few, John Seed, T. Weldon Bellville, Bill Forrest, Bill Beaver and more recently Bob Kaikor.

Dr. Houde has also well served the medical and scientific community by his participation on numerous national and international commissions and boards. Of particular note are his services to The International, American and Eastern Pain Associations and The Committee on Problems of Drug Dependence.

Dr. Houde is a modest, gentle man whose career may be summed up by the following citation:

"Raymond Wilfred Houde -- compassionate physician, brilliant clinical scientist. Your research into the nature of pain and its relief has greatly benefited mankind."

The Committee on Problems of Drug Dependence is honored to name you as the 1984 recipient of The Nathan B. Eddy Award.

The Analgesic Connection: The Nathan B. Eddy Memorial Lecture

Raymond W. Houde

First, I should like to thank the Committee for honoring me with this award. To have been chosen to present the Nathan B. Eddy Memorial Lecture is a very special honor and privilege for me. Dr. Eddy was one of our strongest supporters, and he played an important role in keeping our research team intact and on track. I have very vivid memories of him at these meetings. I can still almost feel his presence down there in the front row - gazing downward in contemplation. At first, I used to think him asleep, but soon learned the folly of that notion in the ensuing discussion period. But he was alway fair with us, and beneath that stern and somber exterior I found him a warm and true friend.

I also want to thank those of you upon whose shoulder I have stood to become visible for this award, and I am most grateful for a most dedicated staff and group of associates. Most of you here know Stan Wallenstein and Ada Rogers who have been with me almost from the start. They and the other members of our research team, including a secretary who has been with me almost as long, are the ones who have kept it all together for these past 30 plus years.

It would be presumptuous for me to explain to you Dr. Eddy's involvement with the analgesic connection. However, I should like to tell you how I became involved, for the circumstances have a bearing on some of the studies we later conducted with the support of this Committee. While serving as a medical resident at Memorial Hospital after my discharge from the Navy at the end of World War II, I was approached by two of our internists who asked me to assist them in a study they had undertaken of some new strong analgesics which had been developed by the Germans during the war. Their study was being carried out in the manner in which studies were usually done then and, too often, are still being done in the same way today. It was conducted as an uncontrolled open trial - and the observations were made in an unsystematic way by the busy floor nurses whose other duties often took precedence over a study in which they had little interest or commitment. Eventually, the time came to put it all together for presentation at a meeting of the New York Academy of Sciences, and you just know who pulled the

short straw (Houde et al., 1948). I did not think then that I did such a bad job under the circumstances - but a sharp-tongued biostatistician named Bliss in the audience thought otherwise, and I can leave it to your imagination as to how well that discussion period went for me. I vowed then and there that I had had it up to here with analgesic studies.

I do not recall whether I had actually met Dr. Eddy then, although he also presented a paper at the meeting which included a rather favorable report of a nationwide survey on the effectiveness of oral metopon (methyldihydromorphinone) in cancer patients. We were among the hundreds of physicians who submitted reports to him, but our five patients must have been among the outliers in his data on over 5,000 patients. But, I was not about to make a point of that! To me, at that time, Dr. Eddy looked every bit as austere and formidable as the good Dr. Bliss.

Sometime later, I was invited to attend a meeting between a number of pharmaceutical company executives - including Maurice Tainter, who chaired the Academy of Sciences meeting - and C.P. Rhoads, Director of the Sloan-Kettering Institute, to set up an analgesic study program at our hospital. Having been once burned, I wanted to have nothing to do with it - but I was later induced to change my mind by being offered a sabbatical and an opportunity to get additional training in pharmacology. It was then my good fortune to have as my mentors, in succession: Drs. Seevers, Harris Isbell and Abe Wikler - who were later to become, in the same sequence, the first three recipients of the Eddy Memorial Award.

My second meeting with Dr. Eddy was in November 1949. I had been invited to attend a meeting of this Committee, known then as the National Research Council Committee on Problems of Drug Addiction and Narcotics, to present a report of the studies I had been carrying out in spinal animals of the tail flick of the rat and skin twitch of the dog and guinea pig, indices of pain commonly used in laboratory animals for testing drugs for analgesic activity. The results of that early work led me to conclude that these methods measured spinal reflexes upon which opiates acted and that they were thus not true measures of the effects of these drugs on pain perception. Rereading that report (Houde, 1949), I am amused by my not-too-profound statement which read as follows:

> Nevertheless comparison of the effect of medication before and after operation showed that invariably the threshold rises were appreciably greater in the intact than in the spinal animal for any given dose of the drugs employed - an observation which we have not been able to fully explain.

A lot of water has passed under that bridge since that split infinitive!

On my return to Memorial Sloan-Kettering, my efforts were directed more to the development of a clinical research program than to my studies with spinal animals, which was then gradually phased out. In the meantime, I had become acquainted with Harry Beecher and impressed by his reports to this Committee at its annual scientific meetings which I have attended regularly since 1951. In 1956, we received the first in a long series of small annual grants from the

Committee which served to keep our research team together and greatly influenced the direction of our research.

Working at a large cancer center has tended to insulate us from some of the problems of drug abuse. But it has also provided unique opportunities to compare the effects of analgesics in a variety of circumstances which have relevance to questions of whether to restrict the use and availability of substances expected to have abuse potential. Most patients with cancer will experience some acute or chronic pain in the course of the disease or its treatment, or from complications of the disease or treatment. Many of these patients will also have organ dysfunction capable of influencing the absorption, distribution, metabolic disposition or elimination of particular analgesic drugs. Moreover, virtually all patients with cancer are subject to a great deal of emotional stress and the manner in which they contend with it will vary with their backgrounds, personalities, and a wide variety of other circumstantial factors. The need for effective analgesic medications for these patients is undeniable and it is unlikely that any single analgesic, or single class of analgesics, will fill the bill. What is desirable or undesirable in an analgesic will be influenced to a great degree by the clinical circumstances. The role of the physician is to relieve both pain and suffering, and side effects which may be considered adverse or undesirable in some situations may be highly desirable in others. The goals of the search for better analgesics are not out of step with those of the quest for nonaddicting or nondependence-producing analgesics. I have no allusions that we will ever find the panacea, but I do believe that substantial progress has and will continue to be made in the development of drugs that are more selective in their actions, or have different constellations of pharmacological actions, to provide greater flexibility in meeting medical needs.

We now recognize that many different classes of drugs are capable of producing dependence, and compulsive drug-seeking behavior has become more closely linked to their euphorigenic or other mood-altering properties than to signs or symptoms of tolerance and physical dependence. But euphoria is hardly an adverse side effect to a patient dying of cancer, even though a sense of well-being may seem inappropriate to the onlooker in that circumstance. Quite understandably, most patients report that they feel better when their pains are relieved and, at least in our studies of the morphine-like opioids, the extent of mood elevation seems to closely parallel the degree of pain relief. As we look across drug classes, however, differences can be seen. This has been most striking when comparing morphine to narcotic agonist-antagonist analgesics - such as nalorphine, pentazocine, nalbuphine and butorphanol - when pain relief was observed despite dysphoric reactions in a substantial proportion of patients (Houde, 1979). With somewhat more sensitive instruments, such as the mood questionnaire which we have been employing recently, nonsteroidal antiinflammatory drugs can also be distinguished from morphine in terms of their relative lack of mood elevating actions in equianalgesic doses. To what extent this constitutes a great leap forward will of course depend upon when and how these drugs are used clinically. The relative potentials or therapeutic indices of

the nonsteroidal analgesics and the narcotic agonist-antagonists are, in general, lower than those of the traditional opiates or morphine-like opioids and, because of their potentially adverse hematological and gastrointestinal side effects, the nonsteroidals are particularly hazardous for some patients - particularly cancer patients receiving chemotherapy.

In pharmacological terms, a statement of relative potency is nothing more than an expression of the ratio of doses of two drugs which produce a given effect. Its major function in the evaluation of analgesics is that it allows one to compare drugs in terms of their side effects, or adverse effects, at equianalgesic doses. On the other hand, when speaking of efficacy, we are primarily concerned with the maximal effect obtainable by increasing the dose to the point of limiting side effects. To denote this, we have used the term 'relative potential'. Maximal or 'ceiling' effects, are demonstrable only if one can demonstrate no further increases in effect with increasing doses (Fig.1). In the clinical setting, we have not found it possible to do this with morphine or its surrogates because limiting side effects intervene before the log dose-response curve flattens out. Although there are certain criteria which must be met for a valid relative potency assay, designing a study in that manner has undeniable advantages. First of all, it forces the use of graded doses of the test or standard drugs, and the responses to graded doses of a standard drug provide a measure of the sensitivity of the assay. We strongly believe that the ability to demonstrate that the subject population and

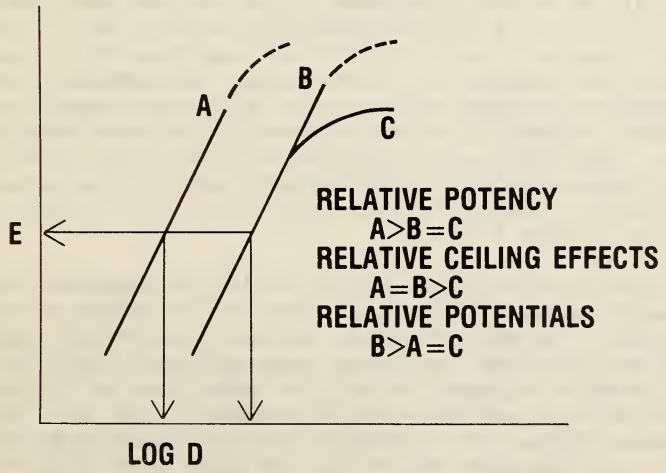

FIGURE 1. Conceptual representation of 'relative potency' 'relative ceiling effects' and 'relative potential'. The solid regression lines of effect on log dose denote responses within limiting adverse effects of hypothetical drugs A, B, and C, and the dashed lines their projections beyond that level.

method are capable of discriminating between a known active standard and a placebo, or between graded doses of the standard, should be an integral part of every study of the effects of drugs on pain.

To illustrate this point, I should like to give a brief report on a series of studies that we carried out with metopon, the long since departed drug which had been the subject of Dr. Eddy's report at the New York Academy of Science meeting in 1948. Pre-clinical and preliminary clinical trials were said to have demonstrated that the oral and parenteral analgesic doses of this drug were essentially the same, that tolerance and dependence developed more slowly than to morphine, and that the drug was relatively free of adverse effects. From the results of the nationwide survey, Dr. Eddy concluded that metopon hydrochloride, which was supplied as a 3 mg capsule, was an effective oral analgesic for chronic pain due to cancer, and that its use was accompanied by a "high incidence of mental clarity and a low incidence of side effects." He also commented that tolerance to metopon developed more slowly than tolerance to morphine. In light of all this, we were intrigued by the fact that the drug was hardly being used at all less than 10 years later.

First we undertook to do a double-blind crossover study comparing graded intramuscular doses of metopon to graded doses of morphine and a placebo in a series of sequentially related experiments in patients with pain due to advanced cancer (Houde and Wallenstein, 1957). In each of these experiments or "quintets", as they were called then, each patient received two doses of metopon which varied in each quintet, 8 and 16 mg of morphine, and a saline placebo, all in a randomized order. The patients were seen hourly during the day by a single nurse, Ada Rogers, who recorded the patients' reports of pain intensity and administered the coded test medication for moderate to severe pain. The patients' responses were evaluated in terms of the areas under the time-effect curves for changes in pain intensity in each of the four experiments or quintets. The data met the statistical requirements for a valid relative potency assay and showed that, indeed, when administered intramuscularly, metopon hydrochloride was over 3.5 times as potent as morphine sulfate (Fig.2).

We then sought to determine whether orally administered metopon is as effective as parenteral metopon when studied double-blind in the same patient. As we had done in an earlier study of aspirin and morphine, double-blind conditions were achieved simply by administering both a capsule to take by mouth and an intramuscular injection when the patient required medication for pain (Houde and Wallenstein, 1958). The results of that study, which was otherwise conducted in the same manner as the comparison with morphine, revealed that metopon was less than 1/5th as potent by mouth as it was by intramuscular injection when tested in the same patients in the same setting, and by the same method, double-blind. When the results were reported to the Committee in 1958, Dr. Eddy was gracious in his remarks but, I suspect, not totally convinced, for shortly after that, he put our method to test in a study, with Lyndon Lee, of the relative potency of parenteral oxymorphone and

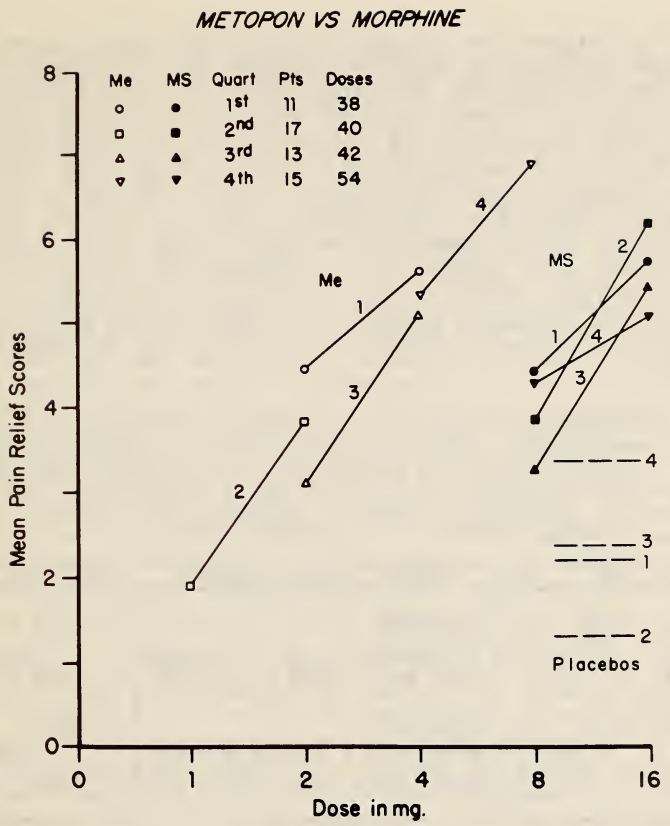

FIGURE 2. Dose response curves for intramuscular metopon and morphine plotted in terms of the mean total scores for changes in pain intensity over 6 hrs (the ordinate) and logarithm of the dose (abscissa) for each of the four quintets, numbered in the order in which they were done. The respective placebo scores are shown as dashed lines.

morphine. We had assayed oxymorphone a few years before and reported to the Committee that we found 1.12 mg of oxymorphone equianalgesic to 10 mg of morphine and that the 95 per cent confidence limits of our estimate were 0.90 to 1.65 (Houde and Wallenstein, 1956). Dr. Lee's study was conducted double-blind in cancer patients at the Wayne County General Hospital in Michigan, but, back in Bethesda, Dr. Eddy controlled the code and determined the dose ratios to be studied. When their results were in, their analyses revealed 1.02 mg of oxymorphone to be equivalent to 10 mg of morphine with 95 per cent confidence limits of their estimate similar to ours (Eddy and Lee, 1959). After that I knew we were in with Dr. Eddy.

We also used the relative potency approach in a small short-term

study of tolerance and cross-tolerance involving intramuscular metopon and morphine in which an estimate of the relative potencies of the two drugs was determined in a small group of patients over a period of a week, and then half the group was placed on repeated doses of morphine and the other half on repeated doses of metopon for 7 to 8 days. Finally, in the third week, the drugs were reevaluated for their relative potency as they had been in the first week (Houde and Wallenstein, 1957). Only 13 patients completed this little experiment, so that it was based on relative potency estimates in only 6 and 7 patients, too few to provide a definitive answer. However, the results were consistent in showing that tolerance did indeed develop to metopon as well as to morphine and that cross-tolerance between the two drugs was not complete.

TABLE I: Approximate equianalgesic mg doses of morphine (Mo) and metopon (Me) based on crossover comparisons of graded doses of each drug before and after chronic administration of each drug in two separate small populations of tolerant patients with advanced cancer.

PRE - Mo	Me	CHRONIC ADMINISTRATION	POST - Mo	Me
mg equiv	10.0	5.1	MORPHINE -	16.8	6.4
rel pot	1.96x		# inj/day = 5.2 x 8.1 days	2.63x	
% change	-- , --		mean daily dose = 77.3 mg	+ 68% , + 25%	
mg equiv	10.0	5.2	METOPON -	22.8	17.0
rel pot	1.92x		# inj/day = 5.96 x 6.8 days	1.34x	
% change	-- , --		mean daily dose = 29.7 mg	+ 128% , + 227%	

A similar study comparing methadone and morphine in a still smaller group of 11 patients revealed a similar result. Because of the relatively short length of stays of patients in active treatment hospitals such as ours, it is extremely difficult to get together a sufficient number of relatively stable patients for more definitive studies of tolerance and physical dependence. However, it is possible to identify patients who are relatively nontolerant and others who are obviously tolerant to opioids, merely on the basis of their recent past drug experience and the amount of drug that they require for pain relief. It has, thus, been possible for us to carry out parallel studies in two populations using the same methodology and nurse-observers. This procedure has been particularly useful in looking at interactions of agonist-antagonists, such as pentazocine and morphine, where distinctly different patterns are observed. In nontolerant patients, the effects of the two drugs were found to be essentially additive, whereas in tolerant patients, increasing the ratio of pentazocine to morphine not only produced a progressive decrement in the analgesic effect of the combination to the point of providing no analgesia but also of precipitating withdrawal signs in some patients - an indication that analgesic tolerance and physical dependence to narcotics go hand in hand.

Employing the same strategy, we undertook to test the hypothesis that, because of its reported greater euphorigenic properties, heroin would prove to be uniquely effective in patients with advanced cancer. To do this we carried out parallel studies in nontolerant patients undergoing potentially curative surgery and in narcotic tolerant patients with hopelessly advanced incurable cancer. The drugs were administered intramuscularly and the studies differed from those I have just described only in that we employed visual analog scales in addition to our verbal categorical scales of pain intensity and pain relief, and we also included both a visual analog scale and a word pair questionnaire (adapted from Lasagna et al., 1955) for measuring mood effects. The results confirmed what was already well documented in the medical literature, namely, that heroin is approximately twice as potent as morphine on a milligram basis, and that it has an earlier onset and shorter duration of action than morphine. Moreover, though the chronic pain patients with advanced cancer obtained less relief than the postoperative patients from comparable doses of both drugs, the analgesic potency of heroin relative to morphine was found to be virtually the same in the two patient populations. Also of interest was the fact that the effects on mood paralleled the analgesic data, and this was shown very convincingly by the results of the mood questionnaire (Kaiko et al., 1981).

We have, also, recently completed a double-blind comparison of the relative oral to intramuscular potency of heroin hydrochloride which revealed that it requires about 10 to 12 times as much heroin by mouth to produce the same effect as when it is given by intramuscular injection. Based on our earlier studies of the oral/parenteral potency of morphine in which we found that it required almost six times as much oral morphine as intramuscular morphine to produce the same analgesic effect (Houde et al., 1965), it appeared to us that essentially all of the heroin given by mouth was being converted to morphine before reaching the central nervous system. That, in fact, was what we found in later studies of the bioavailability of oral heroin since, when it was given by mouth in doses as high as 60 mg, all that we were able to detect in the blood was morphine, by an analytical assay method sensitive to 1 to 2 ng/ml of heroin or 6-monoacetylmorphine, the other major metabolite of heroin. On the basis of these results, it would seem that administering heroin by mouth is simply an expensive way of administering morphine which itself undergoes fairly extensive first-pass metabolism. The failure to detect any striking differences in the euphorigenic properties of intramuscular heroin and morphine also leads me to believe that the passage of the bills now in Congress to legalize heroin are more likely to compound the problems of the DEA than to improve the management of the dying cancer patient. As has also been recently reported (Inturrisi et al., 1984), heroin does not bind to the opiate receptor, and its central actions are believed to be due to its being converted to 6-monoacetylmorphine and morphine.

I should prefer not to close on this negative note. Actually, substantial progress has been made in developing drugs that have

brought us closer to Dr. Eddy's dream. Of perhaps greater importance, the strides made in understanding the neuropsychophysiological causes of pain have, in large measure, resulted from that search for a strong nonaddicting analgesic and investigations of the mechanisms of actions of the narcotic analgesics. Earlier Eddy Award winners - specifically Bill Martin, Hans Kosterlitz, Eddie Way, Avram Goldstein and Eric Simon - have all given you sterling accounts of that research and it would be foolhardy for me to venture into that territory. However, I hope that with these few examples of my involvement with Dr. Eddy's dream, I may have been able to throw a bit of light on some of the more commonplace aspects of the analgesic connection between the problems of drug abuse and legitimate medical concerns.

Lastly, I should like again to thank the Awards Committee and all of you for your forbearance in accompanying me in my journey down memory lane.

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Opiate and Opioid Modulation of Reproductive Endocrinology in the Male and Female: Development and Pregestational Aspects

Theodore J. Cicero

In this review, the influence of opiate drugs on reproductive endocrinology in the male and female rodent will be reviewed. Additionally, the possible role, and physiological significance, of endogenous opioid peptidergic systems in modulating activity in the regulatory systems involved in the release of luteinizing hormone (LH) and LH-releasing hormone (LHRH) will also be evaluated. The review has been divided into three major sections. In the first, the influence of opiate drugs on reproductive endocrine parameters will be discussed, particularly with respect to how the natural evolution of these studies led to the hypothesis that endogenous opioids represent an integral component of the hypothalamic circuitry involved in LH/LHRH release. Second, the age- and sex-related differences in the opioid-mediated control of reproductive endocrinology will also be evaluated within the context that opioid peptides may be involved in the onset of puberty and sexual maturation. Finally, several recent studies will be discussed in which the neuroendocrine maturation of offspring derived from drug-naive females and males treated pregestationally with opiates have been examined.

INFLUENCE OF OPIATES ON THE HYPOTHALAMIC-PITUITARY-GONADAL (H-P-G) AXIS

Over the past 10 years, the effects of opiate drugs on the H-P-G axis have been extensively examined in both the male and female of virtually every species. To summarize this large body of literature would not be possible here, but several recent studies are available (Cicero 1980; Kalra 1982; Kalra and Kalra 1983). For the purposes of this discussion, it is important to note only that reproductive endocrinology is disrupted by both acute and chronic opiate drug administration and that these compounds appear to exert their primary effects by inhibiting the release of LHRH from the hypothalamus. The precise manner in which the opiates inhibit the release of LHRH has not been characterized, but it appears that this action is mediated by opiate receptor(s) within the hypothalamus. The existence of opiate receptors within the hypothalamus, which apparently impinge in some fashion on LHRH-

containing cell bodies, has led to the hypothesis that there may be endogenous opioids present to interact with these receptors and, hence, play a role in the complex hypothalamic control mechanisms involved in the release of LHRH. This hypothesis has been impressibly supported by the following observations (which have been fully discussed in the references listed above) (Cicero 1980; Kalra 1982; Kalra and Kalra 1983). First, opiate antagonists produce rapid dose-dependent increases in serum LH levels within minutes after their subcutaneous administration; second, naloxone competitively inhibits steroid-induced negative feedback control of LHRH. Third, several endogenous opioids injected directly into the cerebral ventricles depress serum LH levels, whereas antibodies to several of these peptides increase LH levels. Fourth, manipulations known to alter activity within the hypothalamic-pituitary-LH axis produce changes in endogenous opioid contents in the hypothalamus and pituitary and in opioid receptor topographies. Finally, morphine and other opioids are just as effective as testosterone in reversing the effects of castration on the hypothalamic reserves of LHRH. Taken as a whole, these observations suggest that opioid-containing neuronal pathways represent an important component of the hypothalamic circuitry involved in LHRH release and may represent an intermediate link between the effects of steroids on the hypothalmus and their inhibition LHRH.

DEVELOPMENTAL ASPECTS

The probable role of endogenous opioids in the regulation of reproductive endocrinology has prompted several investigators to examine whether alterations in opioid peptide-containing systems are involved in sexual maturation and the onset of puberty in the male and female rodent (Blank et al. 1979; Blank et al. 1979, 1980; Ieiri et al. 1979; Schulz et al., 1982). In three of these studies, the response to naloxone, an opiate antagonist known to increase LH levels in the adult, has been examined in prepubescent, adolescent and adult male and female rats and the LH-depressing action of morphine has been evaluated in only one study. Aside from this relative paucity of studies, few definitive conclusions can be drawn from these published reports: the results are both qualitatively and quantitatively different.

An inspection of these reports suggests that numerous factors could be involved in these discrepancies, including very small numbers of subjects, the use of non-optimal drug doses and post-injection time intervals and, finally, only selected time intervals during development have been examined. Because developmental studies offer a unique opportunity to more fully understand the relationship of endogenous opioids to the control of LHRH/LH, we have carried out a parametric study examining the age- and sex-related differences in the LH response to a prototypic opiate agonist (morphine) and antagonist (naloxone) in the rat.

Methods

Sprague-Dawley derived male and female rats were bred in our laboratories (F1 generation of animals purchased from Harlan

Industries, Indianapolis, Indiana) and maintained at a constant environment of 22-25°C under a 12-hour light:dark cycle. At 80-90 days of age, one male and female were housed together for two complete estrous cycles, at which time the males were removed and the females permitted to carry to term. The dates of birth of the offspring were recorded to the nearest 12 hours. Litters were culled to 8 pups (4 males and 4 females) at 10 days of age and weaned from their mothers at 21-24 days. Male and female offspring were utilized at the following ages: 10, 15, 20, 25, 30, 35, 40, and 60 days of age. To minimize biological variation and provide sufficient material for the multiple assays to be carried out, we found it necessary to use 45 animals of each sex at days 10, 15, 20 and 25 (blood pooled from 3 animals for a total N of 15) and 15 animals at all older ages. At the appropriate intervals, rats were injected with supramaximal doses of morphine (10 mg/kg), naloxone (1 mg/kg) or saline, as determined in preliminary studies. They were then killed by decapitation 2 hours after the injection of morphine or 20 min after the administration of naloxone, the times at which optimal decreases and increases in serum LH levels, respectively, are found; half of the saline-injected animals were killed at each post-injection time interval to control for possible circadian rhythms. Serum was obtained and frozen at -20°C until LH radioimmunoassays (RIAs) were carried out. Once the foregoing study was completed, an additional experiment was carried out in which morphine and naloxone dose response curves were constructed in both males and females at those intervals when morphine and/or naloxone appeared to be least effective in the preceding studies.

Results

Effects of naloxone and morphine on serum LH levels. The effects of saline, naloxone (1 mg/kg) and morphine (10 mg/kg) on serum LH levels in male rats from 10 to 60 days of age are shown in Figure 1. The data depicted in this figure represent the pooled results of two experiments (N=30 to 40). Neither naloxone nor morphine affected serum LH at the earliest time interval examined (10 days of age) in male pups. However, from 15 days to adulthood (60 days), morphine maximally suppressed LH levels to less than 25% of control values, which was near the limits of detection of the RIA. In marked contrast to these results, naloxone evoked no statistically significant increase in serum LH levels from 10 to 30 days of age and, moreover, at 15 days of age, LH values were significantly lower in naloxone-pretreated rats than they were in controls. After 30 days of age, the LH response to naloxone increased in a linear fashion to adulthood when naloxone-induced increases in serum LH were 500% greater than in control animals (i.e., saline-injected). As shown in figure 2, the patterns of responses to naloxone and morphine were substantially different in females. At 10 through 25 days of age, morphine failed to depress serum LH levels. At 30 days a modest, but significant, suppression of LH occurred which became progressively more intense to adulthood; at 60 days of age LH levels in morphine-pretreated female rats were approximately 60% lower than in controls. Thus, two major sex-related differences in the response to morphine were noted: females displayed a much later onset in appropriate LH response to morphine (30-35 days versus 15 days) and the absolute

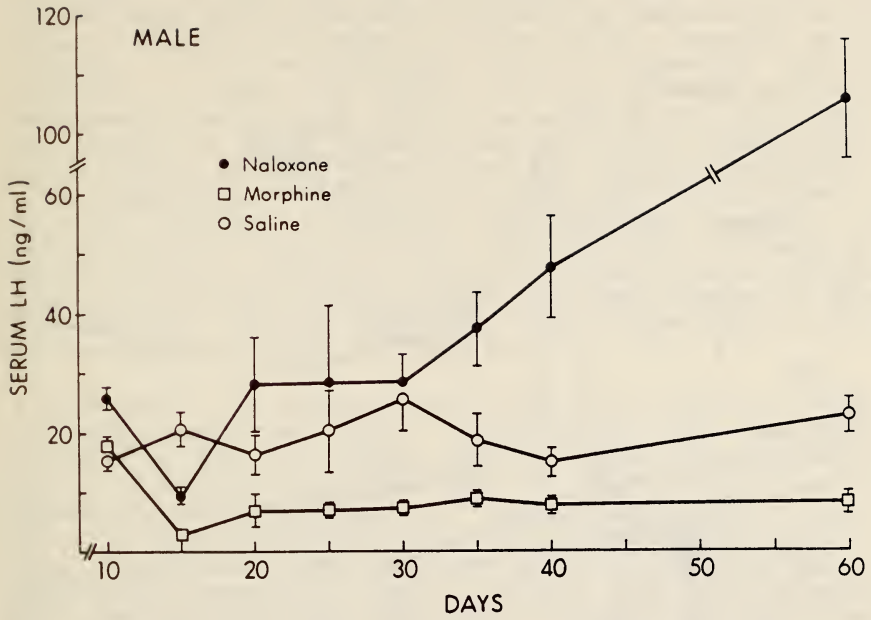

FIGURE 1. The effects of saline, morphine (10 mg/kg) or naloxone (1 mg/kg) on serum LH levels in male rats injected on the days shown after birth.

depressions in LH were substantially less in females than they were in males (50-60% versus >75%). As shown in figure 2, an even more striking sex-related difference was found with naloxone. In contrast to the male, in the female, naloxone produced extremely large increases in serum LH at 10 (highly variable, however) and 25 days which were substantially greater than those observed at any other time point. Interestingly, between days 10 and 25, the antagonist did not influence serum LH levels at all. After the naloxone-induced burst in serum LH levels at 25 days of age, it remained highly effective in increasing LH levels, but the absolute increase in LH declined gradually such that by 40-60 days of age, increases in serum LH levels were only about 50% as large as those observed at 10 or 25 days.

Dose-reponse curves for naloxone and morphine. In the previous studies, only one dose of each drug was employed and animals were killed at only one time interval. Although the doses and post-injection time intervals were selected as optimal ones, the possibility existed that this approach may have obscured the fact that morphine and naloxone were simply less effective, rather than devoid of activity, at the "critical" periods identified. To evaluate this, dose-response curves for naloxone- and morphine-induced changes in LH were constructed at those intervals determined in the preceding studies at which there appeared to be a complete refractoriness to the drugs. Our results demonstrated that at 10 days of age, a point at which morphine (10 mg/kg) was

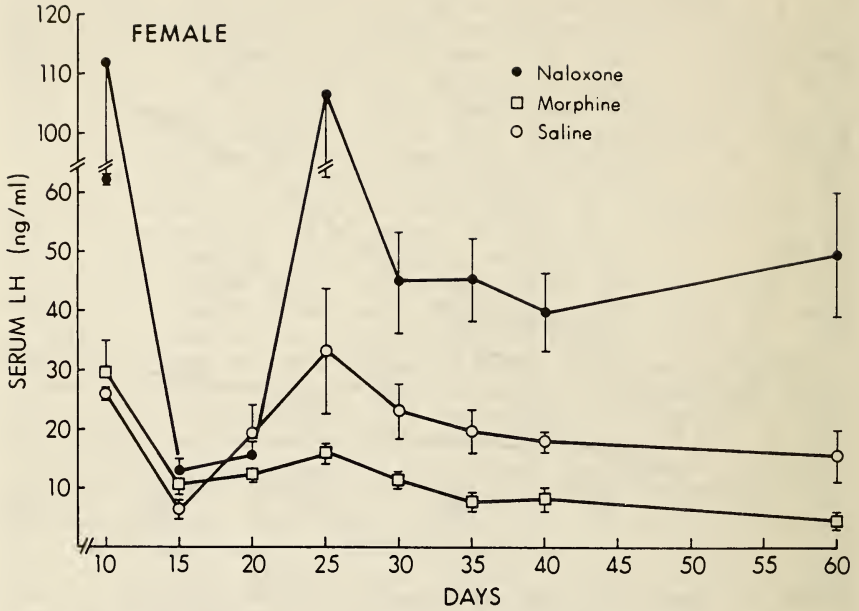

FIGURE 2. Same as legend to Figure 1 except females were utilized.

ineffective in lowering serum LH levels in the male in the previous studies (see figure 1), morphine dose-response curves revealed no effect on LH at 5 or 10 mg/kg, but a significant depression was found at a dose of 25 mg/kg. However, it should be noted that morphine was quite toxic at this dose level, raising a question regarding the significance of this fall in LH. In sharp distinction to these results, morphine failed to depress serum LH levels in 15-day-old females at any dose from 5-25 mg/kg. In agreement with the previous studies (figures 1 and 2), naloxone failed to increase serum LH levels over a wide range of doses in 30-day-old males or 15-day-old females.

Concluding Remarks

The preceding results suggest that the responsitivity of the opioid-mediated control of LHRH varies markedly during sexual maturation and, moreover, is strongly sex-related. Whether our results suggest that opioids are involved in the onset of puberty and sexual maturation cannot be stated with certainty at this time, but the "critical periods" we have identified for the maturation of naloxone and morphine appropriate responses appear to correlate quite well with all other indices of sexual development.
The mechanisms involved in the differential sensitivity to naloxone and morphine in males and females at different points in

development have not been examined at all. However, two obvious possibilities suggest themselves: differential time courses for the appearance and/or functional activity of the relevant opioid receptors or of the endogenous opioid(s) responsible for the regulation of LHRH. No studies have directly examined these relationships per se, but there are a number of reports in which the ontogeny of opioid receptors and opioids have been examined (Unnerstall et al. 1982; Khachaturian et al. 1983). Unfortunately, these studies were not designed to focus on the "critical" periods we have identified. Similarly, the literature regarding the maturation of the H-P-G axis is not particularly germane for several reasons: (a) few studies have examined time periods equivalent to those utilized above; (b) most experiments have examined only selected parameters; and (c) few studies have compared males to females (see Kalra 1983).

A major goal of our current research efforts is to carry out these necessary comparative studies in an effort to more fully characterize the developmental aspects of the opioid-mediated control of reproductive endocrinology. In addition to the obvious significance of these studies at this basic level, our studies could be quite significant from two additional perspectives. First, our results suggest that the developing organism may be particularly susceptible to opiates, or other drugs which influence endogenous-opioid function, during the prepubescent and adolescent periods. Given the increasingly prevalent usage of such compounds in human males and females during these critical points in their sexual development, these experiments could have obvious clinical significance. Second, if it can be demonstrated that specific opioid peptides or opioid receptor subtypes show marked alterations during the onset of puberty and sexual maturation, this could prove to be one of the most definitive means of establishing the identity of the endogenous opioid involved in LHRH release.

PREGESTATIONAL INFLUENCES OF THE OPIATES.

Although there are numerous studies of the adverse effects of the administration of opiates to pregnant females, little attention has focused on the deleterious effects of exposure of males to opiates prior to or during mating. One particularly intriguing series of studies, however, has been carried out by Dr. Gladys Friedler which indicate a potentially important pregestational effect of opiates in male mice (Friedler 1974; Friedler and Crescenzi 1981; Friedler and Wheeling 1979). She has found that exposing males to morphine 1 to 2 weeks prior to mating, followed by a 7-10 day drug-free period, produces a number of anomalies in their offspring. They also differ substantially in their response to opiate agonists and antagonists as adults, but what is most interesting about her studies is that these effects can be generated by as little as one dose of morphine and can be transmitted from one generation to the next.

In collaboration with Dr. Friedler, we have recently completed two studies comparing the reproductive endocrine parameters in opiate-derived adult male offspring versus normal controls (Friedler et al. 1982). Our results are briefly summarized below.

TABLE 1

Effects of Pregestational Morphine or Saline Administration on Reproductive Endocrine Parameters

	Serum LH levels (ng/ml)		Pituitary LH levels (ng/mg protein)	
	Morphine	Saline	Morphine	Saline
Castrate	103.4 ± 17*	361.8 ± 52	18.7 ± 1.2**	15.8 ± 1.8
Sham	24.1 ± 1.8**	30.2 ± 3.7	16.1 ± 1.1**	14.3 ± 1.2

* $p < .01$, ** $p < .05$ when compared to saline-pretreated rats.

Methods

Adult male CD-1 mice, 80-90 days of age, were injected with saline or morphine, 50 mg/kg, twice daily for 8 1/2 days. After a drug free period of an additional 8 1/2 days, the males were mated with drug naive females. Animals were prepared in Dr. Friedler's laboratory, the subsequent offspring were coded by her, so that the neuroendocrine studies could be carried out blind, and shipped to my laboratory at 30-35 days. Only male offspring have been utilized in the studies to date. After a 30-40 day equilibration period in our laboratories, the animals were divided into four groups: saline-derived - sham-operated; saline-derived - castrated; opiate-derived - sham-operated, and opiate-derived - castrated. Forty-eight hours after the appropriate surgical procedure, the animals were killed by decapitation and blood and tissue samples were obtained. The reason for using both sham-operated and short-term castrated animals was that massive deficits in the functional activity of the H-P-G axis would be evident in both groups, whereas more subtle differences might be apparent only in the castrates. The following indices were measured: serum LH and testosterone levels, hypothalamic LHRH content, and pituitary LH content. In addition, opioid receptor profiles in brain and hypothalamus were assessed. Finally, in a preliminary study, we evaluated whether the LH responses of opiate-derived offspring to morphine and/or naloxone were different than those observed in saline-derived offspring.

Results

The results of these studies are briefly summarized in table 1. As can be seen, in opiate-derived adult male offspring, serum LH levels in sham-operated animals were approximately 20% lower than those found in saline-derived offspring, but this deficit was considerally more pronounced in castrated animals. The 10-fold or greater increase in serum LH levels normally produced by castration was significantly attenuated (<60%) in opiate-derived offspring when compared to controls (see table 1) such that serum LH levels were more than 70% lower in this group than they were in controls. Accompanying these changes in serum LH, a modest increase in the pituitary content of LH was observed in morphine-derived animals when compared to controls (table 1). Similarly,

seminal vesicle weights and serum testosterone levels were lower in opiate-derived animals than they were in controls, but neither of these differences was statistically significant; no changes were observed in hypothalamic LHRH (data not shown).

With regard to the opioid-mediated regulation of activity in the hypothalamic-pituitary-LH axis, we found no alterations in μ, kappa and delta receptor populations, respectively, in whole brain or hypothalamus; competition and selective protection studies confirmed these conclusions. On the other hand, in a preliminary study, we observed a significant attenuation of the response to both naloxone and morphine in opiate-derived offspring relative to controls. Unfortunately, insufficient numbers of animals were available to construct appropriate dose-response curves.

Concluding Remarks

The preceding results reinforce the prior conclusions of Friedler and her colleagues (Friedler 1974; Friedler and Crescenzi 1981; Friedler et al. 1982) that pregestational opiate administration to the male produces a number of adverse effects in their offspring. The profound neuroendocrine disturbances we have observed in the present studies represent perhaps the most significant anomalies yet found in opiate-derived offspring and suggest that pregestational opiate administration to males produces substantial and pervasive effects on the structural, biochemical and functional integrity of their subsequent offspring. Although previous studies have shown that opiates are quite toxic to developing fetuses when given to pregnant females, the present results, and the earlier work of Friedler et al.(1974, 1981, 1982), suggest that pregestational opiate administration may be just as harmful and, most significantly, that variables influencing the male at some time prior to conception may be as important, or more important, than those influencing the pregestational or gestating female. One additional point should be emphasized in the studies of Friedler and her colleagues. Specifically, she has noted that the adverse effects she observes are not only evident in the F1 generation, but can be transmitted from one generation to the next. These intriguing observations defy a rational explanation at this time, but have profound implications. We have no information as yet as to whether the neuroendocrine effects we have observed in the present studies can be passed along to subsequent generations or for that matter if fertility and/or the capacity to fertilize is affected.

With respect to the mechanisms involved in the pregestational effects of the opiates, two interrelated phenomena must be explained: what are the factors involved in the initial opiate-induced insult to the male parent; and what are the mechanisms involved in the neuroendocrine deficits found in their offspring? There is a complete void in the literature on both points. However, in an ongoing series of studies in our laboratories we are examining the influence of opiates on mature sperm. The rationale for this strategy is that the treatment paradigm used by Dr. Friedler involves administration of opiates 8-12 days prior to mating. At this time, sperm in the vas deferens are fully mature

and are stored there for up to 3 weeks before ejaculation. Thus, it seems reasonable to postulate that adult sperm are adversely affected by the administration of opiates. Although there is no definitive evidence relevant to this point, several observations suggest that opiates may indeed influence mature sperm function. For example, it has been shown that opioid receptors are prevalent in the reproductive tract, that opiates are found in semen after their administration and, finally, that opioid peptides occur in semen, the testes and the secondary sex organs (Cox and Baizman 1982; Margioris et al. 1983; Shaha 1984; Sharp and Pekary 1981; Tsong et al. 1982) These observations indicate, at the very least, that opiates can readily gain access to sperm and could potentially exert adverse effects. In this connection, it should be noted that in 1975 we found that methadone-maintained patients and heroin addicts had significantly reduced sperm motility (>75%) when compared to controls and a significant percentage of the sperm were dead (Cicero et al. 1975).

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Acute Effects of Marijuana on Pituitary and Gonadal Hormones During the Periovulatory Phase of the Menstrual Cycle

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INTRODUCTION

Experimental animal studies have demonstrated that pituitary and gonadal hormones essential for normal female reproductive function are altered by acute administration of cannabis compounds. Dose-dependent suppression (1 to 5 mg/kg) of luteinizing hormone (LH) occurred within 1 h after acute administration of Δ^9-tetrahydrocannabinol (THC) to ovariectimized rats (Marks 1973). Lower doses of THC (62.5 mcg/kg) reduced LH concentrations by 42 to 68% in ovariectimized rats (Tyrey 1980). THC (5 mg/kg) also inhibited the periovulatory LH surge in intact rats and delayed ovulation for up to 24 hours (Nir et al. 1973).

An intramuscular dose (2.5 mg/kg) of THC suppressed plasma LH levels for 12 to 24 h in ovariectimized rhesus monkeys (Asch et al. 1979). The magnitude of LH suppression was not correlated with THC dose but the duration of LH suppression was dose related (Smith et al. 1979a, b).

Acute doses (2 to 16 mg/kg) of THC produced decrements in plasma prolactin levels in normal (Chakravarty et al. 1975) and ovariectimized female rats (Hughes et al. 1981). Prolactin surges induced in female rats by electrical stimulation of the cervix were delayed by intravenous administration of 4 mg/kg of THC (Hughes and Tyrey 1982). THC administration also suppressed suckling-induced prolactin surges in female rats (Tyrey and Hughes 1983).

A brief suppression of prolactin levels in male and female rhesus monkey occurred after THC administration (Asch et al. 1979). THC suppression of prolactin secretion was reversed by thyrotropin releasing hormone which directly stimulates prolactin release from the pituitary (Asch et al. 1979). Administration of gonadotropin releasing hormone (GnRH) restored normal ovulation in THC-treated rats and also reversed THC inhibition of LH in monkey (Smith et al. 1979a; Nir et al. 1973). These data converge to suggest that THC inhibitory effects on pituitary release of LH are due to drug effects upon hypothalamic neurons involved in

regulation of pituitary hormone secretion.

Although there have been many studies of THC effects on reproductive hormones in human males (Bloch 1983), there are relatively few data concerning cannabis effects on female reproductive hormones. We have been able to locate only one study on effects of marijuana smoking on pituitary and gonadal hormones in human females. Bauman and coworkers (1979) conducted an outpatient evaluation of 26 women, who reported marijuana use at least 4 times per week and 16 age-matched controls who never used marijuana. Blood samples were collected on days 1, 5, 10, 12 to 18, 20, 25, and 30 of the menstrual cycle. Marijuana users reported shorter menstrual cycles and shorter luteal phases than controls. No significant changes were found in LH or estradiol levels in marijuana smokers when compared to nonsmokers. However, prolactin levels were lower in marijuana users. A major problem in evaluating these data is that the study was carried out under outpatient conditions where it was not possible to control for self-administration of alcohol and other psychotropic drugs which might also affect pituitary and gonadal hormone homeostasis.

Recently, we reported that acute marijuana smoking suppresses plasma LH levels in women during the luteal phase of the menstrual cycle (Mendelson et al. 1984). Prolactin levels following marijuana smoking also were significantly suppressed during the luteal phase of the menstrual cycle (Mendelson et al. 1984).

The purpose of the present study was to determine the acute effects of marijuana smoking on LH, estradiol, progesterone, and prolactin in healthy adult female volunteers during the periovulatory phase of the menstrual cycle. The women were studied on a residential research ward to ensure that concurrent drug or alcohol self-administration did not occur. This control is important since there is considerable evidence that chronic alcohol abuse disrupts the menstrual cycle (Hugues et al. 1981; Mello et al. 1983; Moskovic 1975) and that opiates inhibit secretion of pituitary gonadotrophins and suppress gonadal steroid hormones (Cicero 1980).

METHODS

Eight healthy adult females provided informed consent for participation in this study. These women were between 21 to 33 years (mean age 26) and their mean frequency of marijuana use was 14 times per month. All had normal physical examinations, medical and mental history evaluations and normal laboratory (biochemistry and hemogram) studies. No subject had any past or current history of alcohol or drug abuse and urine screens for drugs (opiates, barbiturates, tranquilizers, stimulants and depressants) were negative upon admission to the ward. All women reported normal menstrual cycles and none used birth control medication or intrauterine devices. No women had received any form of prescription medication for at least one year prior to the study and none had ever received gonadotrphins or steroids. Subjects were not pregnant as determined by the hCG beta subunit test.

Marijuana cigarette administration and plasma sampling procedures for pituitary gonadal hormones were identical for all subjects. Subjects did not consume food for 12 h prior to the initiation of each study which was begun at approximately 9:00 a.m. An indwelling intravenous cannula with a heparin lock was connected to a slow infusion of 5% dextrose in saline. Baseline blood specimens were collected at 30 min intervals for 120 consecutive min prior to administration of marijuana or placebo.

After baseline samples were collected, each woman smoked a 1-g marijuana cigarette containing 1.8% Δ^9-THC. Standardized marijuana cigarettes were provided by the National Institute on Drug Abuse. Subjects were instructed to take a deep inhalation of the marijuana cigarette once every 30 sec and retain the inhaled smoke for 2-4 sec. Under these conditions, subjects smoked the 1-g marijuana cigarette within 10 to 12 min.

Blood samples were collected at 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 min after initiation of marijuana smoking. Blood samples were centrifuged immediately following collection and aliquots of plasma were stored at -70° C. for subsequent analysis of LH, estradiol, and progesterone.

In order to determine effects of marijuana smoking on naloxone-stimulated LH, 5 mg of intravenous naloxone was infused over 10 min at the same time as marijuana or placebo cigarette smoking in 2 women. Conditions of blood sampling and cigarette smoking were identical to those described above. Placebo cigarettes were provided by NIDA.

LH was assayed as described previously (Mendelson et al. 1978). Results are expressed as ng LER-907 standard ml/plasma. Mean intra- and interassay CV's were 7 and 11%. Progesterone was assayed without solvent extraction using kits purchased from Radioassay Systems Laboratories, Inc., Carson, CA. The mean intra-assay CV was 8.6%. Interassay CV's were 7.0 and 13.6% for controls that averaged 27.6 and 1.12 ng/ml. Estradiol-17β was assayed without extraction using kits purchased from Serono Laboratories, Inc., Randolph, MA. Intra- and interassay CV's were 6.0 and 7.3%.

RESULTS

Figure 1 shows LH, prolactin, estradiol and progesterone levels prior to and following marijuana smoking. A 2-way analysis of variance (ANOVA), with time as a repeated measure, revealed that LH and prolactin levels decreased significantly ($p < .01$) as a function of time. However, ANOVA also revealed a main effect of marijuana smoking on plasma LH and prolactin levels. A small but statistically significant pulse in LH and prolactin levels occurred 20 min after initiation of marijuana smoking and persisted for 45 min following marijuana smoking ($p < .01$) There were no significant changes in plasma estradiol or progesterone levels following marijuana smoking when compared with presmoking values.

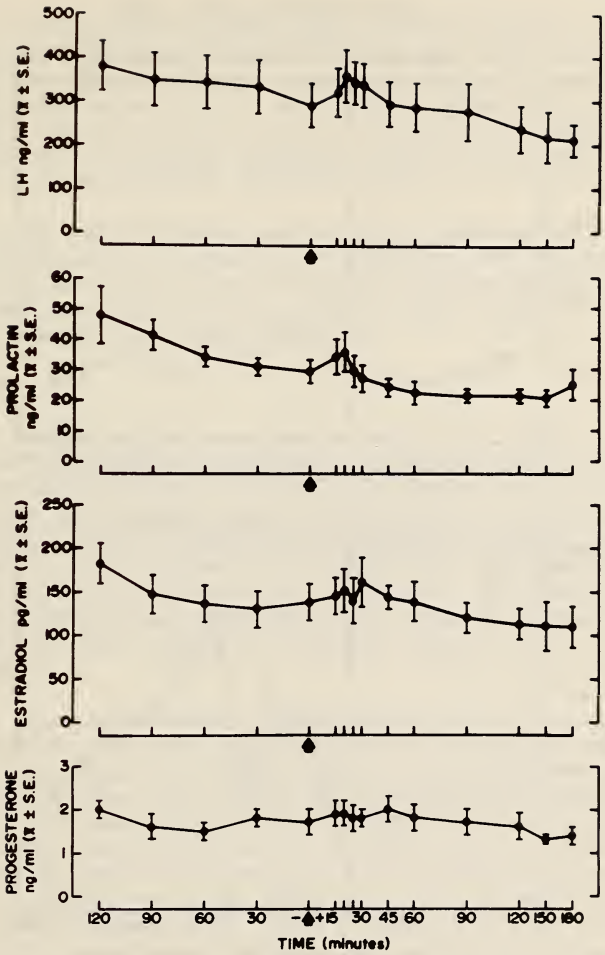

FIGURE 1: LH, prolactin, estradiol, and progesterone levels ($\bar{X}$ ± S.E.) prior to and folloiwng marijuana cigarette smoking during the periovulatory phase of the menstrual cycle. ◆ indicates time of initiation of marijuana smoking.

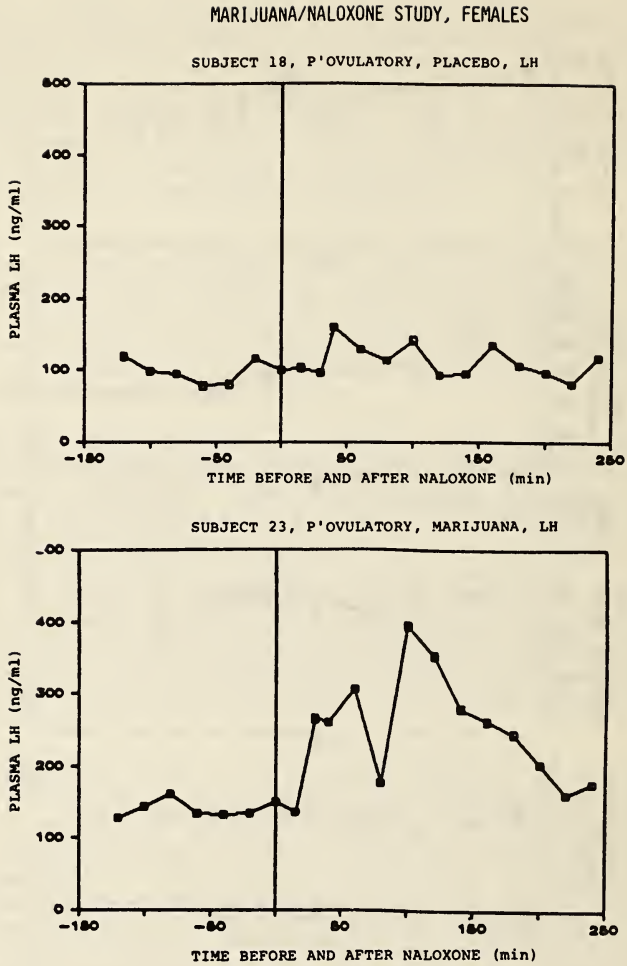

FIGURE 2: Plasma LH levels prior to and after IV naloxone (5 mg) administration. Top panel (subject 18) - smoked marijuana placebo cigarette concurrent with IV naloxone administration. Bottom panel (subject 23) - smoked active marijuana cigarette (1 g containing 1.8% Δ^9-THC) concurrent with naloxone administration.

Figure 2 shows plasma LH levels prior to and following concurrent administration of intravenous naloxone (5 mg) and acute marijuana or placebo marijuana smoking. Intravenous naloxone produced a significant increase ($p < .01$) in LH levels from 100 to almost 150 ng/ml. The initial increment in LH levels following naloxone administration and placebo marijuana cigarette smoking occurred at 45 min and secondary LH pulses occurred at 100 and 120 min.

When naloxone administration and marijuana smoking occurred concurrently, LH levels increased ($p < .001$) from approximately 100 to 250 mg/ml in 30 min. Two secondary LH pulses following concurrent marijuana and naloxone administration peaked at 300 and 400 ng/ml respectively within 120 min.

DISCUSSION

Smoking a single marijuana cigarette containing 1.83% THC produced a small but significant increment in LH and prolactin levels during the periovulatory phase of the menstrual cycle. LH levels prior to marijuana smoking were in the 400 ng range and were consistent with peak ovulatory LH pulse values recorded in normal females of child bearing age. The small but significant marijuana-related increment in LH and prolactin levels observed when basal LH levels were high suggests that relatively small amounts of pyrolized marijuana leaf have a strong stimulatory effect on LH and prolactin release.

LH values prior to naloxone administration were in the 100 ng range and were consistent with levels found in normal women during the early ascending or descending phase of the periovulatory LH surge. This is the first report that naloxone stimulates LH during the periovulatory phase of the menstrual cycle. These findings are surprising since previous studies using a continuous infusion of naloxone indicate that LH is insensitive to naloxone stimulation during the early and late follicular phase (Quigley and Yen 1980; Quigley et al. 1980; Blankstein et al. 1981). Most investigators have found that LH is most sensitive to naloxone stimulation during the luteal phase of the menstrual cycle (Ropert et al. 1981; Quigley and Yen 1980) and it has been suggested that mid-cycle estrogen elevations increase the inhibition of LH by endogenous opioid peptides and diminish the naloxone stimulatory effect (Yen 1980). The apparent discrepancy between our findings and previous reports probably can be reconciled by the fact that we administered naloxone when LH levels were already elevated in the periovulatory phase. Under these conditions, acute naloxone administration produced a significant increase in LH.

The striking increment of LH levels following naloxone administration and current marijuana smoking suggests that cannabis compounds may potentiate effects of gonadotrophin-releasing hormone during the periovulatory menstrual cycle phase. Further studies will be necessary to determine if this effect is specific for THC or may be induced by other cannabis compounds in pyrolized marijuana leaf. Additional studies are necessary to determine the site of action

of cannabis-induced potentiation of LH secretion during ovulation. If cannabis compounds reliably potentiate LH secretory activity during the periovulatory phase of the menstrual cycle, such compounds may be efficacious for the treatment of some forms of infertility in women.

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Feminization in Alcoholic Liver Disease: The Role of Ethanol and Alcoholic Liver Disease

David H. Van Thiel; Judith S. Gavaler; and Patricia K. Eagon

The following is a discussion of our present understanding of the process of feminization of men with advanced alcoholic liver disease.

The first major step in our knowledge about this process was its recognition as a process distinct from that of hypogonadism (Van Thiel 1979). Specifically, alcoholic men with advanced alcoholic liver disease (Laennec's cirrhosis) are both hypogonadal and feminized. For feminization to occur, both chronic alcohol abuse and advanced alcoholic liver disease must co-exist. Moreover, hypogonadism is almost, if not always, a co-existing problem in such feminized alcoholic men. In contrast, alcoholic men can manifest overt hypogonadism in the virtual absence of any biochemical and/or histologic evidence of either alcoholic liver disease or feminization (Van Thiel et al. 1974; Van Thiel and Lester 1976). Thus alcohol abuse per se leads to male hypogonadism. Feminization requires both alcohol abuse and alcoholic liver disease. Males with advanced nonalcoholic liver disease are not feminized except very late in their disease course at a point in time when they are essentially preterminal (Van Thiel 1979). Moreover, rats with carbon tetrachloride-induced cirrhosis are neither hypogonadal nor feminized (Van Thiel 1980a). In contrast, alcohol-fed male rats with minimal liver disease (fatty change) manifest severe gonadal failure (Van Thiel et al. 1975; Van Thiel et al. 1979).

The manifestation of hypogonadism present in alcoholic men are shown in table 1. Both advanced testicular atrophy and reduced testosterone levels as shown in figure 1 are characteristic findings in such chronic alcoholic men and frequently occur as noted above in the virtual absence of important liver disease (Van Thiel et al. 1974; Van Thiel and Lester 1976). Similar findings of testicular atrophy, loss of reproductive tissue, and reduced testosterone levels can be produced in either weanling or adult male rats fed 5% alcohol which accounts for only 36% of their total caloric intake but not in isocalorically matched control animals (Van Thiel et al. 1975; Van Thiel et al. 1979). The alcohol-fed rat model does not develop alcoholic hepatitis, hepatic fibrosis

TABLE 1

Manifestations of Hypogonadism in Alcoholic Men

testicular atrophy
  reproductive failure
  reduced testosterone levels
prostate and seminal vesicle atrophy
reduced beard growth
reduced body hair (particularly sexual hair)
loss of muscle mass
"normal" to elevated gonadotropin levels

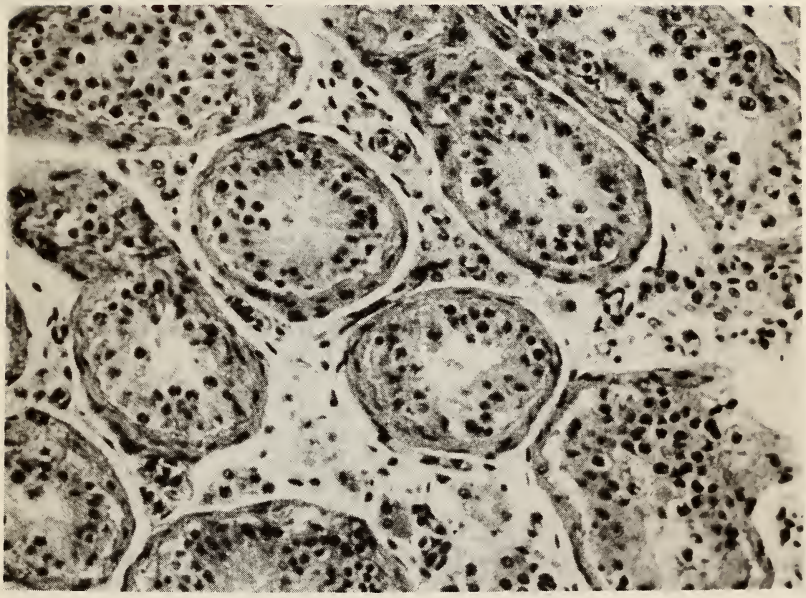

FIGURE 1A

Testicular histopathology in an alcoholic without liver disease but with testicular atrophy H&E X 250.

or cirrhosis but does manifest alcohol-induced hypogonadism. Thus alcohol abuse per se, and not alcoholic liver disease, is the precursor abnormality for alcohol-induced hypogonadism.

Feminization of alcohol-fed male rats does not develop with this model. Moreover, it is not apparent either in man or in experimental animals in the absence of advanced (cirrhotic) nonalcoholic liver disease. The manifestation of feminization seen in alcoholic men with cirrhosis are shown in table 2.

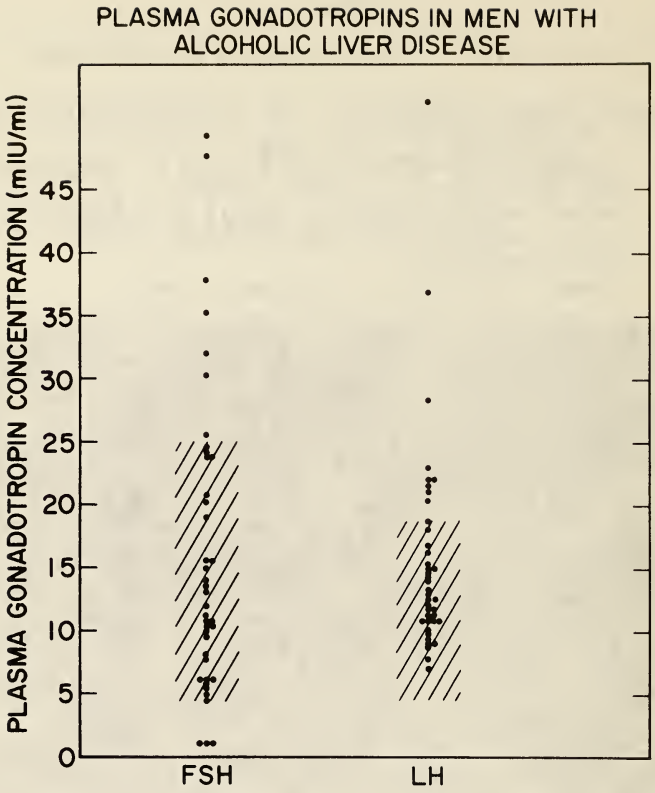

FIGURE 1B

Plasma sex steroid levels in alcoholic men. The cross hatched area is the normal range. Points represent values for alcoholic men.

TABLE 2

Manifestations of Feminization in Alcoholic Men

Biologic	Biochemical
gynecomastia	variably increased levels of estrogens
palmar erythema	increases in prolactin levels
spider angiomata	increases in sex steroid binding globulin levels
female escutcheon	increases in estrogen stimulated neurophysin levels
body fat redistribution	increases in most transport proteins (alpha and beta globulins)

When present in nonalcoholics these signs of feminization occur very late in the course of the disease (preterminal) and are

never as apparent as they are in alcoholics (Van Thiel 1979). What is it then that distinguishes alcoholic liver disease from nonalcoholic liver disease? What characteristics do alcoholics with established cirrhotic liver disease have that alcoholics without such liver disease lack? Finally, what are the biochemical events that effect estrogenization (feminization) and how does alcoholic and nonalcoholic liver disease alter (amplify) this process?

I. Mechanism of Estrogen Action

The presently accepted model of how steroid hormones like estrogens effect their biological effects is shown in figure 2. The

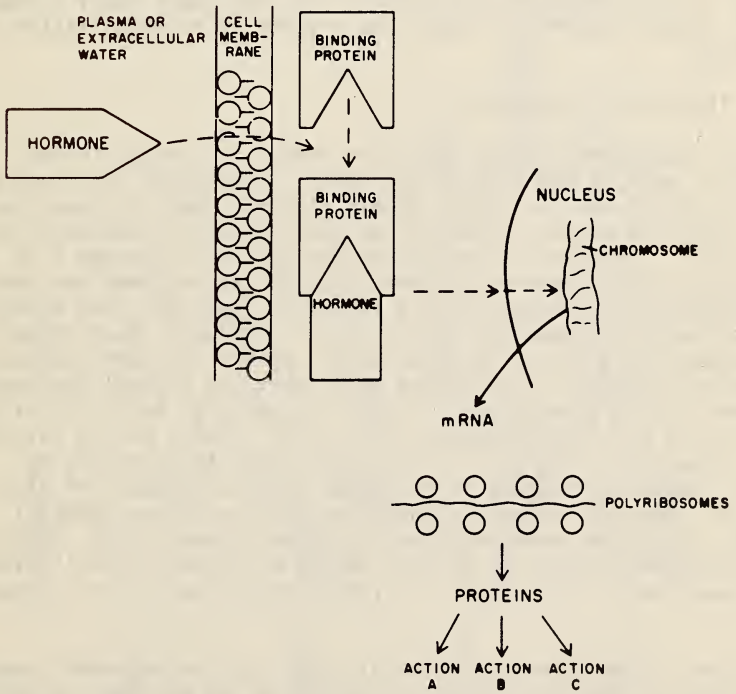

FIGURE 2

Schematic representative of how estradiol acts to produce feminization (an estrogen effect).

lipophilic steroidal estrogen is produced by an endocrine organ or tissue and circulates in the blood both in the bound (BE) and free (FE) form. The vast majority of the plasma estrogen is protein bound but it is the small fraction of free hormone which is available for interaction with and stimulation of steroid responsive tissues. At the level of the steroid responsive tissue, the free estrogen readily diffuses across the lipid plasma membrane and

enters the cytosol. Once within the cytosol, it interacts with a variety of cytosolic proteins, one of which is the estrogen receptor (ER). The receptor protein characteristically has a high affinity and low capacity for its ligand. In contrast, the other estrogen binding proteins in cytosol have both a lesser affinity and greater capacity for estrogen binding. As a consequence of estrogen and receptor interaction, a transformational change occurs in the receptor protein that allows it to be transported across the nuclear membrane with its steroid ligand (ERE). Within the nucleus the complex interacts with DNA. As a result of this interaction, the transcription of specific genes or RNA characteristic of the specific hormonal effect, estrogenization occurs. The mRNA so formed is transformed out of the nucleus and effects the translation of a specific gene product (usually a protein) in the endoplasmic reticulum. The resultant newly synthesized protein actually effects the process of estrogenization of the cell.

II. The Role of Alcoholism

Alcohol ingestion results in a wide number of changes in the liver as well as the rest of the body. Relevant to the present discussion is the fact that chronic alcohol ingestion leads to the induction of the microsomal enzyme, aromatase (Gordon et al. 1979a,b). Aromatase is the enzyme complex that converts C-19 androgens (testosterone) and proandrogens (androstenedione and dehydroepiandrosterone) to C-18 estrogens (estradiol and estrone respectively) (figure 3). Gordon et al. (1979a,b) have shown that regardless of the specific nature of the androgen substrate, aromatase activity is increased as a result of alcohol feeding. As most of the aromatase activity in the body is in skin, fat and muscle and not in the liver or body sites drained by the splanchnic circulation, the conversion of androgens to estrogens by those nonhepatic tissues is increased as a consequence of alcoholism. However, because alcoholism produces primary gonadal failure in the absence of alcoholic liver disease, this induction of aromatase activity by alcohol merely maintains "normal" plasma estrogen levels in the face of overt androgen deficiency (figure 1B).

Additional consequences of alcohol abuse and its attendant hypogonadism are that the cytosolic content of the estrogen receptor is increased and that of the nonreceptor estrogen binding proteins, particularly the male specific binding protein (MSBP) is reduced. As a result, for any given cytosolic level of estrogen, more estrogen is available for binding with the receptor and less opportunity exists for nonreceptor interaction. The net result is an amplification of the estrogen message delivered to the cell (nucleus) for any plasma and cytosolic level of the hormone. It is important to note additionally at this point that only steroidal estrogens bind to the MSBP and other nonreceptor estrogen binding proteins while both steroidal and nonsteroidal estrogens bind to the estrogen receptor (Eagon et al. 1980; 1981).

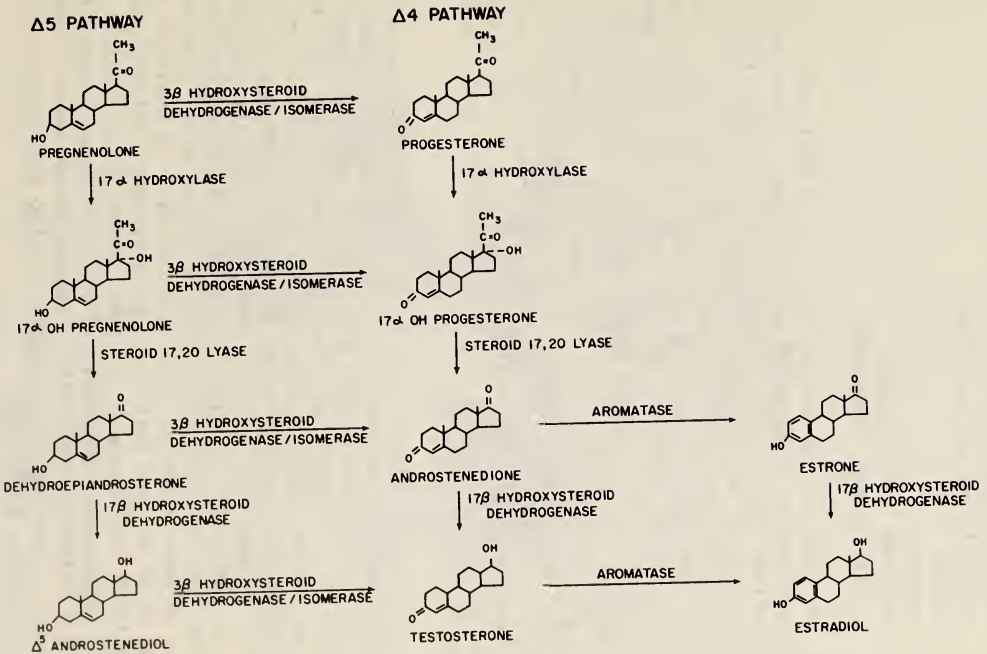

FIGURE 3

Schematic metabolic map showing the conversion of androgens and their precursors to estrogens.

Finally, it must be remembered that alcoholics do not drink ethanol but rather, they ingest alcohol-(ethanol) containing beverages. Such beverages contain many substances other than ethanol which are collectively termed "congeners" as well as the ethanol. Table 3 shows a partial listing of the many kinds of substances which comprise the recognized "congener" substances.

TABLE 3

Congener Substances Identified in Alcoholic Beverages

various aldehydes
various ketones
alcohol esters
various ethers
alcohols other than ethanol
salts
sugars
various organic acids
miscellaneous compounds

Recently we have considered the possibility that among the many congener substances might exist phytoestrogens (nonsteroidal estrogens derived from plants) (Gavaler and Van Thiel 1983). In this regard, it is well known that the major sources of phytoestrogens are seeds and grasses, the same materials which make up the bulk of the nutrient material present in alcoholic beverages. In addition, it is generally the case that ethanol has been the solvent used to extract these phytoestrogens from their original plant sources. Moreover, it should be added that phytoestrogens not only can be found in alcoholic beverages as a result of their leaching out of the grasses and seeds from which such beverages are made but also can be added during the fermentation process and some may be added purposefully as part of the aging process (leached out of wood casks) or can be added for their flavor or coloring characteristics.

This question of whether or not alcoholic beverages contain phytoestrogens has been addressed initially by examining de-ethanolized bourbon for an estrogenic effect using castrate female animals. In this rat model fed de-ethanolized bourbon, any increase in uterine weight and/or suppression of castrate levels of LH would suggest the presence of an estrogenic substance in the material. Indeed, both effects were found (Gavaler and Van Thiel 1983). In subsequent studies, using de-ethanolized bourbon, we have shown that it displaces radiolabeled estradiol from estrogen receptor isolated from rat liver and uterus. In addition, we have been able to show that the phytoestrogens, daidzen and biochanin A (both isoflavanes) obtained commercially displace estradiol from these same receptors. Finally, we have accumulated preliminary evidence that both formononetin and beta sistosterol are present in de-ethanolized bourbon using gas chromatography - mass spectroscopy techniques.

III. The Role of Alcoholic Liver Disease

As discussed above, cirrhosis alone is not sufficient to produce feminization (Van Thiel 1979). This fact is clearly demonstrated by the failure of men with postnecrotic and biliary cirrhosis to demonstrate evidence of feminization and the failure of male rats with carbon tetrachloride-induced cirrhosis to have either increased estradiol levels or reduced LH levels. In contrast, animals with portal hypertension and portosystemic shunting but without cirrhosis have increased estrone and estradiol levels (Van Thiel 1980b). This suggests that it is not cirrhosis but rather the associated portosystemic shunting that leads to increased estrogen levels and feminization in men with Laennec's cirrhosis. Such men also have increased aromatase activity in nonhepatic tissues such as fat, muscle, skin and possibly even the brain due to their primary alcohol abuse. Portosystemic shunting in such men allows for biliary excreted progestins and proandrogens and possibly ingested phytoestrogens to escape hepatic clearance upon being re-absorbed from the gut and instead allows them to circulate to peripheral extrahepatic sites where aromatase exists and allows them to be converted to and act as estrogens (figure 4).

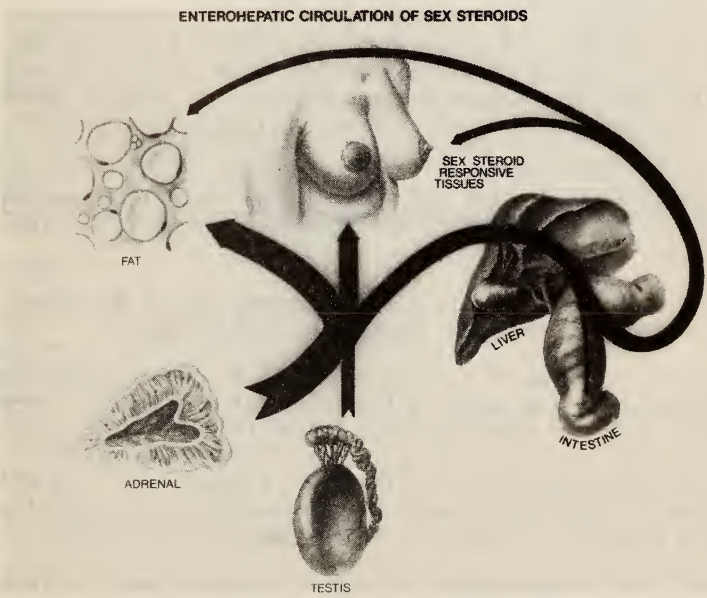

FIGURE 4

Schematic representative of the interrupted enterohepatic circulation in men with cirrhosis and portal hypertension.

It must be remembered also that men with Laennec's cirrhosis are not only cirrhotic and have portosystemic shunts, but also are

alcoholic and have many, if not all, of the factors identified above under the discussion of alcohol effects as well. Thus they have an increased production of estrogen from androgen precursors, a loss of cytosolic nonreceptor estrogen binding proteins, and an enhancement of the cytosolic content of estrogen receptor protein. These many factors, each acting alone as well as in concert, contribute to the observed feminization. Thus cirrhosis and more correctly portosystemic shunting allows the alcoholic with cirrhosis not only to achieve paradoxically "normal" estradiol levels in the face of androgen deficiency but to achieve an actual estrogen excess. This estrogen excess, coupled with the alterations described for the cytosolic estrogen binding proteins produced as a result of alcohol abuse per se and the alcohol-induced hypogonadism, all further amplify the estrogen effect and result in the clinical manifestations of feminization or hyperestrogenization.

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Effects of Delta-9-Tetrahydrocannabinol on Reproductive Neuroendocrine Function in the Female: Animal Studies

Lee Tyrey and Laura L. Murphy

There is now abundant evidence that exposure to delta-9-tetrahydrocannabinol (THC), the primary psychoactive cannabinoid of marijuana, can result in pronounced changes in the secretion of anterior pituitary hormones. While the secretion of each of the anterior pituitary hormones is to some extent influenced by THC (see Braude and Ludford 1984), much of the recent research effort has focused on those hormones which regulate reproduction. The motivation for this focus has arisen in large measure from questions regarding the possible reproductive consequences in humans from prolonged or repetitive THC exposure through chronic use of marijuana, particularly since that use is concentrated in age groups in or approaching their prime reproductive years. The possibility of effects on reproduction may have particular relevance to the female since normal ovarian function is critically dependent upon appropriate cyclic variations in the secretion of pituitary gonadotropins.

While there is no completely adequate substitute for well-controlled studies with human subjects in establishing the endocrine effects of marijuana use by humans, animal experimentation aids the formulation of hypotheses for testing with human subjects and plays an essential role in addressing basic issues, such as mechanism of action, where human studies are not feasible. A variety of animal models have been utilized to good advantage by different investigators, but the laboratory rat may possess particular value in this regard because of the wealth of fundamental background information which has accumulated from years of reproductive neuroendocrine research with this species. That which follows is intended to illustrate some of the ways in which this animal model has been manipulated to probe the effects of THC on pituitary function, focusing upon the acute effects of THC on luteinizing hormone (LH) and prolactin (PRL) secretion in the female. There is no attempt to provide a general review for which the interested reader is referred to a recent monograph published by the National Institute on Drug Abuse (Braude and Ludford 1984).

LH AND PRL SECRETION IN THE RAT

Before proceeding to a discussion of the effects of THC on the pituitary reproductive hormones, there are several aspects of the regulation of these hormones in the rat worthy of mention. During most of the four- or five-day period of the estrous cycle, the secretion of LH and PRL is held at a relatively low level and is comparable to the secretion of these hormones in the male. However, in the female this low "tonic" secretion is interrupted in cyclic fashion by abrupt increases in the secretion of both LH and PRL which, in spontaneous ovulators like the rat, are attributed to the positive feedback effect of estrogen secreted from preovulatory ovarian follicles. These cyclic "surges" represent a stimulated mode of secretion which does not occur in the male and which is generally considered to be governed by regulatory processes distinct from those regulating tonic secretion.

In the case of PRL, additional forms of stimulated secretion are recognized in the rat which are characteristically different from that which occurs during the normal estrous cycle. Stimulation of the uterine cervix around the time of ovulation, such as would occur with mating or mechanical probing of the vagina, reflexly provokes the secretion of PRL in a series of diurnal and nocturnal surges which occur twice daily for 10 or 11 days (Freeman et al. 1974; Smith and Neill 1976). These PRL surges act to prolong the life of the corpora lutea during early pregnancy. In the event of infertile mating or following artificial stimulation of the cervix the prolonged luteal function establishes a state referred to as pseudopregnancy.

Another form of stimulated PRL secretion, common to both the rat and the human, occurs in the lactating female in response to suckling. This neuroendocrine reflex differs from that occurring with cervical stimulation in the sense that the suckling reflex requires reapplication of the stimulus for each induced response, whereas with cervical stimulation a single application of the stimulus induces a series of responses continuing for several days. Thus not only do the tonic and surge modes of hormone secretion appear to be under differential regulation, but the different forms of surge secretion also are likely to be governed by different regulatory mechanisms functioning within the central nervous system (CNS).

Just as the secretory patterns for LH and PRL appear to be regulated differently, the manner in which secretion is controlled by the hypothalamus is distinctly different for these two hormones. The secretion of LH is stimulated through the action of gonadotropin releasing hormone (GnRH) secreted into the hypophysial portal circulation from nerve endings in the median eminence. Increasing the level of GnRH stimulation at the level of the pituitary thus provokes an increase in LH secretion (Sarkar et al. 1976; Sherwood and Fink 1980). PRL secretion, on the other hand, is tonically inhibited by the hypothalamus through the action of one or more PRL inhibiting factors (PIF's) released into

the portal circulation, of which one is believed to be dopamine (Neill 1980). A surge in PRL secretion therefore presumably results at least in part from withdrawal of this tonic inhibition, although the stimulative action of an as yet unidentified physiological PRL releasing factor may also be involved. These basic differences in the regulation of LH and PRL secretion should be borne in mind during the following discussion of THC effects on the serum concentrations of these two hormones.

EFFECTS ON TONIC HORMONE SECRETION

The detection of possible inhibitory effects on the tonic secretion of LH in the female rat is complicated by the fact that LH secretion is already very low during the intervals between cyclic preovulatory surges of LH. A suitable model can be created, however, when the negative steroid feedback on LH secretion is interrupted by ovariectomy. The resulting exaggerated episodic secretory pulses and tonically elevated serum LH concentration provide a system which seems ideally suited for the detection of potential inhibitory effects on LH secretion.

When ovariectomized rats fitted with indwelling atrial cannulae were treated intravenously (iv) with THC during an interval when blood samples were obtained every 10 min, the complete inhibition of episodic LH secretory pulses and a consequent rapid decline in serum LH concentration were readily apparent (Tyrey 1978; 1980). The LH suppressive effect quickly followed acute iv treatment with THC in doses of 0.5 to 8 mg/kg body weight (b.w.) , but it should be noted that a similar inhibition, although of briefer duration, has been observed following acute treatment with THC in doses down to and including 62.5 ug/kg b.w. (Tyrey 1980). Treatment with the vehicle used to deliver the THC, 10% propylene glycol and 1% Tween 80 in saline, had no notable effect on either the episodic secretion or serum concentration of LH. In general, a dose-response relationship could not be established for the degree of LH suppression produced by THC treatment, although such a relationship was evident for the duration of suppressed secretion. Similar findings have been reported for the monkey (Besch et al. 1977).

The tonic secretion of PRL also is suppressed in the ovariectomized rat following acute treatment with THC. The administration of THC in iv doses of 0.25 to 8 mg/kg b.w. resulted in a pronounced reduction in the concentrations of PRL measured in serum obtained 1 hr after treatment (Hughes et al. 1981). While the 0.25 mg/kg b.w. dose produced less inhibition at 1 hr than did the higher doses, it should not be concluded that the lowest dose of THC was less effective in reducing PRL secretion since the difference at 1 hr could merely reflect a rebound of PRL secretion from an earlier more pronounced suppression in these animals. A time course study with THC at 0.5 mg/kg b.w., the lowest dose which was maximally effective at 1 hr, revealed that PRL secretion was rapidly suppressed after drug administration in that a significant decline in serum PRL concentration was already apparent 10 min after injection of even this relatively modest

dose of THC (Hughes et al. 1981).

EFFECTS ON HORMONE SURGES

Several years ago Nir et al. (1973), and later Ayalon et al. (1977), convincingly demonstrated that the preovulatory surge in LH secretion which occurs spontaneously during the afternoon of proestrus in the rat can be blocked by appropriately timed treatment with THC. When THC in a dose of approximately 10 mg/kg b.w. was administered intraperitoneally (ip) prior to the expected time of the LH surge, either as a single injection (Ayalon et al. 1977) or divided into two equal doses administered 2 hrs apart (Nir et al. 1973), the LH surge was effectively blocked and the ovulation expected that night was prevented. Spontaneous ovulation occurred in these blocked rats the following night, approximately 24 hrs after the expected time.

The rise in serum PRL which occurs at the time of the gonadotropin surge during the afternoon of proestrus also is blocked by THC administered (ip) in doses of approximately 10 mg/kg b.w. (Ayalon et al. 1977). However, suppression of this proestrous PRL surge has been seen after treatment with much lower doses of THC administered via the iv route. Even though the proestrous PRL surge was already underway, a single iv injection of THC in a dose of 0.5 mg/kg b.w. was quickly followed by an abrupt and pronounced fall in the serum PRL concentration (Hughes et al. 1984).

The suppression of stimulated hormone secretion by THC is not unique to the estrogen-dependent surges occurring during proestrus since other modes of stimulated PRL secretion are inhibited by acute exposure to THC. The effect of THC on the nocturnal PRL surges occurring during pseudopregnancy was studied in rats in which pseudopregnancies were induced by electrical stimulation of the uterine cervix at the time of estrus (Hughes and Tyrey 1982). Single iv injections of relatively large doses of THC (4 mg/kg b.w.) just prior to the time of an expected nocturnal surge delayed the onset of the surge by approximately 1 hr. However, when THC exposure was extended by hourly injections of THC in lower doses (1 mg/kg b.w.) throughout the interval of the expected PRL rise, the surge was prevented altogether.

The effect of THC on stimulated PRL secretion induced in the lactating mother by the suckling stimulus may be of particular importance since this neuroendocrine reflex plays a critical role in the maintenance of milk production. The treatment of lactating rats with THC in single iv doses of 0.5 mg/kg b.w. prevented the suckling-induced PRL surge in the majority of animals when the drug was administered just prior to the onset of suckling (Tyrey and Hughes 1984). Even when the reflex surge in PRL secretion was already underway as the result of suckling prior to the administration of THC, the PRL surge was nonetheless inhibited and serum PRL concentrations declined in spite of continued suckling by the pups (Tyrey and Hughes 1984).

LACK OF DIRECT PITUITARY EFFECTS

The simplest, most direct explanation which might account for the ability of THC to inhibit the secretion of both LH and PRL in both tonic and surge modes of release would be the direct inhibition of hormone secretion at the level of the pituitary. The experimental evidence, however, provides little support for that hypothesis (Tyrey 1984). In the ovariectomized rat, exogenous GnRH injected as an iv bolus during the time of maximal LH suppression induced by prior THC treatment (1 mg/kg b.w.) provoked an immediate LH surge of considerable magnitude (Tyrey 1978). This result, which is consistent with those from other species (Smith et al. 1979; Asch et al. 1979), indicates that the pituitary remains responsive to the releasing activity of GnRH during THC-induced LH suppression, but, of course, does not rule out the possibility of an attenuation of that response. The latter seems unlikely, however, since the LH response induced in THC-treated rats by a moderate dose of GnRH (50 ng/kg b.w.) was comparable to that produced by an equivalent dose administered to ovariectomized rats pretreated with estrogen and progesterone, rather than THC, to suppress the elevated serum LH levels (Tyrey 1978). The steroid-pretreated ovariectomized rat is acutely sensitive to the releasing action of GnRH and has been utilized for the bioassay of GnRH activity (Ramirez and McCann 1963).

In the case of PRL, the unavailability of an accepted physiological releasing hormone has required a somewhat different approach to testing for possible direct pituitary inhibitory effects. Advantage was taken of the fact that PRL secretion from anterior pituitary tissue removed from hypothalamic control dramatically increases as a consequence of freedom from tonic inhibition. When hypophysectomized female rats bearing ectopic anterior pituitary grafts beneath the kidney capsule were treated (iv) with THC in a dose (1 mg/kg b.w.) which was maximally effective in suppressing PRL secretion from the *in situ* pituitary, no reduction in serum PRL concentrations was observed (Hughes et al. 1981). Although THC similarly failed to demonstrate any direct inhibition of PRL secretion from anterior pituitary tissue incubated *in vitro* (Hughes et al. 1981), the *in vivo* results are important since they provide evidence that neither THC itself nor a circulating active metabolite acts directly on the pituitary to inhibit PRL secretion.

CENTRAL NEUROENDOCRINE EFFECTS

Neurons which secrete the releasing and inhibiting hormones regulating anterior pituitary function terminate throughout the outer zone of the median eminence in conjunction with the primary capillary loops of the hypophysial portal circulation. Since THC does not have any pronounced effect at the pituitary level, it seems reasonable to conclude that the drug alters pituitary function through effects on the release of the hypothalamic hormones into the portal circulation. How this might be accomplished, of course, remains to be explained, but clearly could involve action at several possible levels. At the most fundamental level, THC could act directly on the neurosecretory neuron in a way which might, for example, alter the hormone

release mechanism at the axon terminal, alter the intraneuronal transmission of the signal for that release, or even alter the threshold for initiation of that signal within the neuron. Alternatively, and perhaps more likely in view of the diversity of THC's neuroendocrine actions, the drug could affect, directly or indirectly, the function of neurons which converge on the neurosecretory units to modulate their level of functional activity. Clearly, identifying the level(s), and ultimately the mechanism(s), of THC's inhibitory effects on LH and PRL secretion will be a difficult task, but the rat may prove especially valuable in this area and some initial probes already have been made utilizing this animal model.

The measurement of LH released in response to direct brain stimulation was utilized to address the question of whether or not endogenous GnRH release could be provoked during THC-induced LH suppression. Earlier work had indicated that stimulation of the medial preoptic area (mPOA) of the brain overcomes blockade of the proestrous LH surge induced by a variety of drugs with different pharmacological actions (Everett and Tyrey 1982). When cyclic female rats were treated (ip) with a dose of THC (10 mg/kg b.w.) which was sufficient to block the spontaneous LH surge and then subjected to mPOA stimulation, an unambiguous LH surge was recorded during the subsequent 90 min. Furthermore, the LH surge induced by the preoptic stimulation was adequate to bring about full ovulation in the majority of animals so stimulated. No ovulations were recorded in control animals blocked with THC and subjected to sham stimulation which included placement of the electrode in the mPOA without the passage of current. While these preliminary results from an ongoing study do not yet rule out the possibility of some attenuation of responsiveness to stimulation, they do indicate that the GnRH neurons remain responsive to activation and are capable of a presumptive discharge of GnRH sufficient to induce an LH surge during that time when the spontaneous discharge of this signal to the pituitary is apparently blocked by THC action. Since the intensity of mPOA stimulation was relatively modest (Velasco and Rothchild 1973), it seems unlikely that THC has any major blocking effect on transmission of the release stimulus to the median eminence nerve terminals or on the local release mechanism discharging GnRH from those terminals.

The possibility that THC might inhibit PRL secretion through some action in the median eminence, perhaps, for example, by promoting an increased release of PIF, was investigated in animals subjected to surgical deafferentation of the medial basal hypothalamus (MBH). This approach took advantage of the observation by others that the MBH could be disconnected from the remainder of the brain without interrupting the tonic inhibitory control exerted over PRL secretion by the hypothalamus (Blake et al. 1972; Turpen and Dunn 1976). If THC acts directly on the neurosecretory elements which continue to function in the surviving hypothalamic "island" to maintain the tonic inhibition of PRL secretion, it might be expected that THC would continue to exert an inhibitory effect on PRL secretion in animals subjected to MBH deafferentation.

However, a study utilizing rats subjected to complete deafferentation of the MBH failed to provide evidence for a decrease in serum PRL concentration following the iv administration of THC in a dose of 0.5 mg/kg b.w. (Hughes et al. 1984), a dose which maximally inhibited PRL secretion in nonlesioned animals (Hughes et al. 1981). Companion studies in which only partial deafferentation of the MBH was produced in cyclic rats by frontal cuts placed in the suprachiasmatic region similarly resulted in a loss of the PRL suppressive effect following THC administration (Hughes et al. 1984). Cuts in this region were intended to interrupt afferent pathways into the MBH from more rostral PRL regulatory centers believed to be particularly involved in the regulation of PRL surges (Neill 1980). The results obtained thus far make it unlikely that THC acts directly on the presumptive PIF secreting neurons of the MBH, but rather suggest that the PRL inhibitory effect exerted by THC depends upon rostral connections to the MBH, perhaps from the postulated rostral regulatory centers. It also should be noted that, surprisingly, more rostral transections in the suprachiamastic region not only prevented the THC-induced suppression of PRL secretion, but also resulted in a preparation wherein serum PRL increased immediately after THC administration (Hughes et al. 1984). A similar PRL rise following THC treatment also has been observed in ovariectomized rats subjected to frontal cuts in the suprachiasmatic region (unpublished observations). While the significance of this unexpected PRL stimulatory effect of THC in lesioned animals remains to be explained, it is possible that removal of a dominant inhibitory effect allows a stimulatory action to be expressed.

SUMMARY

The rat experimental model has been utilized to demonstrate pronounced suppressive effects of THC on the secretion of both LH and PRL, a point of considerable interest since the tonic secretions of these two hormones are regulated in opposite fashions, that of LH requiring active stimulation, and that of PRL, continued inhibition. Moreover, both the tonic and surge modes of secretion of both hormones are inhibited or completely blocked by THC action even though these different secretory modes are presumed to be governed by different CNS regulatory mechanisms. The most direct explanation for this broad inhibitory capability of THC would be direct inhibitory action on the pituitary cells secreting LH and PRL. However, experimental evidence drawn from the rat model, consistent with that from other species, provides no support for the possibility of direct pituitary inhibition of significant consequence. Instead, the evidence strongly favors the hypothesis that THC exerts its neuroendocrine action centrally and thereby influences pituitary function through alterations in the release of hypothalamic hormones into the hypophysial portal circulation.

With the evidence favoring a central neuroendocrine mechanism for THC action, the rat model becomes particularly valuable because of the enormous body of information already available regarding

neuroendocrine function in that species. Initial experiments with the rat have failed to provide evidence supporting the possibility of direct THC action on the hypothalamic neurosecretory neurons terminating in the median eminence. Rather, the retention of GnRH release capability during THC-induced LH suppression and the apparent dependence of THC-induced PRL suppression on rostral connections to the MBH are observations consistent with the possibility of THC action at sites removed from the neurosecretory neurons themselves. Thus, while definitive conclusions are not yet possible, it seems reasonable that THC may act to alter the activity of neuronal systems which normally serve to modulate the functional level of neurosecretory neurons in the MBH. If this is the case, potential sites of action through which THC might influence pituitary function are not limited to the hypothalamic region since THC effects could be conveyed into the MBH over afferent pathways arising in widely distributed regions of the CNS. In the case of PRL, the critical pathway may approach the MBH from the rostral direction.

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Progress Report From the NIDA Addiction Research Center (Preclinical Laboratory), Lexington, Kentucky (1984)

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This is the last annual report from the Lexington facility of the ARC. By mid-July the unit will have transferred to the newly remodeled facility of the ARC at Baltimore City Hospitals, where we will join our clinical colleagues; and by the end of the summer, after 49 years of continuous operation at that site, we will have closed out the Lexington facility. We hope you will all join us next year to visit the new ARC, the dedication of which will be held in conjunction with the meeting of the CPDD.

As in recent past years, I will review briefly this afternoon several ongoing projects from our laboratory.

β-ENDORPHIN-LIKE IMMUNOREACTIVITY IN HUMAN CENTENARIANS

For several years the Sanders-Brown Research Center on Aging at the University of Kentucky and the Office of the Governor have engaged in a joint program to identify and recognize centenarians in the state. About 1 1/2 years ago the Center organized a broad multidisciplinary study to investigate a number of biological and social characteristics associated with the extreme longevity of this unique group. We are participating in this study with an interest in looking at present drug-taking patterns and also plasma levels of β-endorphin-like immunoreactivity in this group. This afternoon I will report briefly on early results of the endorphin study.

Because of the large number of blood studies to be done on these subjects we could obtain no more than 0.5 ml of plasma. Therefore, our first problem, and the one on which I will concentrate in this report, was development of methodology sufficiently sensitive for determination of β-endorphin-like immunoreactivity in small sample volumes. Most published methods, especially those separating endorphin from lipotropin, use large sample volumes, some as great as 20 ml. Based on preliminary information supplied by New England Nuclear, an extraction procedure was developed using three c.c. C18 Bond-Elut solid phase extraction tubes fitted with filtration columns with an appropriate vacuum manifold. The tubes were conditioned by pretreatment with methanol containing

0.2% trifluoroacetic acid (TFA), 4X1 ml, followed by water with 0.1% TFA. Plasma samples of 0.1 to 1.0 ml containing 0.5% TFA were added and the columns washed with water with 0.1% TFA, 2X1 ml. β-Endorphin was eluted into small polypropylene tubes with 1.5 ml of methanol containing 0.5% TFA, and the extracts were evaporated to dryness at room temperature under nitrogen.

β-Endorphin-like immunoreactivity was determined by radioimmunoassay carried out in the tube containing the dried extract. The I^{125} RIA kit from New England Nuclear was used with some modification in the provided procedure. All steps of the assay were carried out at 4°C using an ice bath, cold room, and refrigerated centrifuge; silanized glassware or polypropylene was used throughout. The extract was reconstituted with 0.1 ml of assay buffer and 0.1 ml of antiserum (diluted to give B_0 of approx. 40% bound) added with brief mixing on a Vortex mixer. Samples were then preincubated for 72 hrs. in the cold followed by addition of 0.1 ml of I^{125} β-endorphin and a further 24 hrs. incubation. 0.5 ml of charcoal suspension was then added to precipitate free radiolabeled marker. After a 15-min incubation and centrifugation the total supernatant was decanted and bound radioactivity counted in a gamma counter. The standard curve ran from 1.25 to 25 pg per assay tube; data were analyzed by using a log-logit transformation and constructing a linear curve. Using an 0.5 ml plasma sample the sensitivity corresponding to the 1.25 pg added standard was 10 pg/ml of plasma, representing overall extraction and detection efficiency of approx. 26%. Concentrations below 10 pg/ml could be calculated, but were below the lowest run standard.

β-Endorphin-like immunoreactivity has now been determined by this method in 23 centenarians; their ages range from 100-102 with mean of 100.8 yrs.; 10 are male and 13 female. Mean concentration of β-endorphin-like immunoreactivity was 16.7 pg/ml with a range of a calculated 2.1 pg/ml to 34.7 pg/ml. Although there is a great deal of variability in reported methodologies and subject groups, this appears to be within the range of reported normal values, although probably near the lower end. We are continuing to analyze this data and to accrue additional subjects.

COMPARATIVE METABOLISM OF 6-KETO OPIOIDS

During the last 5 years, we have been engaged in a comprehensive study of the comparative metabolism of 6-keto opioids in humans and several animal species. We studied the metabolism of 4 agonists (hydromorphone, hydrocodone, oxymorphone, and oxycodone) and 2 antagonists (naltrexone and naloxone) in 6 human subjects and dogs, rats, guinea pigs, and rabbits. The urinary excretion of the parent compound and identifiable metabolites was measured over the course of 6 days for humans and 2-3 days for animals. The study is now sufficiently completed that some generalizations have begun to emerge. From the mean human data it is apparent that small structural differences greatly influenced the metabolic profile. The change from N-allyl (in naloxone) to N-cyclopropyl-

methyl (in naltrexone) caused the drug to go from being metabolized primarily to an inactive conjugate (naloxone glucuronide) to being metabolized also in large amounts by keto-reduction to an active metabolite (6β-naltrexol), which may partially account for naltrexone's oral efficacy. Changes from 3-phenolic (as in hydromorphone and oxymorphone) to 3-O-methyl (as in hydrocodone and oxycodone) greatly decreased the role of conjugation, increased the role of N-demethylation, and increased the excretion of free intact parent drug. Also, in going from 3-phenolic compounds, which were selectively reduced to the 6-β alcohol configuration, to 3-O-methyl compounds, the stereoselectivity was completely abolished and a 1:1 ratio of 6β- to 6α-alcohols was produced during 6-keto reduction.

Comparative studies in laboratory animals in the six 6-keto opioids have revealed some overall species trends in the metabolism of these compounds. Humans showed a balanced metabolic profile, with all pathways participating (conjugation, N-dealkylation, O-dealkylation, 6-keto-reduction). The rat showed weak to absent conjugation, N-dealkylation, and 6-keto reduction, and, in general, appears to be a poor model for studying metabolism of these compounds. The dog was an excellent conjugator with moderate N-dealkylation and weak to absent other pathways. The guinea pig was a very good 6-keto reducer, a poor dealkylator and moderate in other pathways. The rabbit was generally balanced across most pathways and appeared to resemble the human profile more closely than the other species. The oxycodone data showed that N-dealkylation does occur in the rabbit. It is apparent that there are metabolic differences among all the species studied and within species there are definitive trends across all 6 drugs. Completion of the full analysis of the oxycodone data will complete this study.

BEHAVIORAL PROPERTIES OF FENCAMFAMINE

Fencamfamine is a sympathomimetic central stimulant which has recently appeared in the illicit drug market of the U.S. and is being considered for scheduling by the World Health Organization. At the last meeting of this Committee, we presented the results of preliminary experiments demonstrating that fencamfamine maintains i.v. self-administration behavior by beagle dogs. Additional experiments to further characterize the behavioral properties of fencamfamine have been conducted during the past year, and the results are summarized in this report.

In the first experiment, the direct effects of fencamfamine on schedule-controlled responding were studied. Four rats responded under a multiple fixed-interval (FI) 300 sec, fixed-ratio (FR) 20 schedule of water presentation. Sessions were conducted daily, Monday through Friday, with each rat. Each session consisted of 10 FI components alternating with 10 FR components. Five doses of fencamfamine (0.1-10.0 mg/kg, i.p.) and six doses of cocaine (0.1-30.0 mg/kg, i.p.) were tested. Drugs were typically

administered on Tuesdays and Fridays; saline control injections were given on Thursdays. Each dose was tested twice in each rat.

Fencamfamine and cocaine produced qualitatively similar effects on performance under the multiple FI FR schedule of water presentation. During the FI components, overall response rates first increased, then decreased with increasing doses of either drug. Peak increases were produced by 30.0 mg/kg fencamfamine and 10.0 mg/kg cocaine. During the FR components, overall response rates were not appreciably different from saline until the highest dose of each drug was tested, at which time responding was almost completely eliminated. The time course of drug effect was also similar for fencamfamine and cocaine. Both drugs had relatively rapid onsets of action, with similar declines over the remainder of the session.

In the second experiment, the discriminative stimulus properties of fencamfamine were studied. Four rats were trained to discriminate cocaine from saline in a two-lever drug discrimination task on a fixed-ratio (FR) 10 schedule of water presentation. I.P. injections of cocaine (3.0 mg/kg) or saline (0.1 ml/kg) were given daily on a double alternation schedule. Each session began with a 5-min blackout period, and was followed by 20 trials, or 30-min, whichever occurred first. Trials were completed when the rat made 10 consecutive responses on the correct choice lever. Responses on the drug-appropriate lever produced reinforcement following cocaine injections, while responses on the opposite lever produced reinforcement following saline injections.

Following acquisition of criterion performance (90% or greater responses on the correct choice lever for eight consecutive sessions), drug testing began. Four doses of fencamfamine and cocaine (0.3-3.0 mg/kg) were tested; saline was also included in the series. Ten consecutive responses on either lever produced reinforcement during test sessions. Both fencamfamine and cocaine produced dose-related increases in the percentage of responses made on the cocaine-appropriate choice lever; fencamfamine was approximately 1.5 times as potent as cocaine in producing cocaine-like discriminative stimuli. Both drugs moderately increased response rates above saline control values; only a dose of 3.0 mg/kg cocaine slightly decreased rates.

In the third experiment, the effects of dopamine blockade on fencamfamine self-administration were studied. Three purebred beagle dogs, with histories of i.v. drug self-administration, were given access to response-contingent drug injections under a fixed-ratio with limited hold schedule of reinforcement. Experimental sessions were conducted daily, Monday through Friday. Each session consisted of 11 trials, each trial lasting a maximum of 4 min; successive trials were separated by timeout periods of 10 min. During each trial, the 15th pedal-pressing response produced a 15-sec i.v. drug injection. Each of five doses of fencamfamine and cocaine (0.01-1.0 mg/kg) were tested for five consecutive sessions, with treatment order arbitrarily determined

for each dog. Following completion of the dose-effect curves, the effects of presession treatment with the dopamine antagonist, pimozide, on fencamfamine and cocaine self-administration were assessed. Pimozide (30.0 mcg/kg, i.v.) was given 30 min before the start of each session for five consecutive sessions for each of the four doses of fencamfamine or cocaine (0.03-3.0 mg/kg).

Both fencamfamine and cocaine maintained self-administration above saline control levels. There was an inverted U-shaped relationship between the number of injections per session and dose per injection; overall rates of responding and local rates of responding were also systematically related to dose per injection, first increasing, then decreasing with increasing doses of drug. For both response rate measures, at least one dose of fencamfamine maintained higher rates than did cocaine. Presession treatment with pimozide shifted the ascending portion of the dose-effect curves approximately one-half log unit to the right; the descending portion of the curves was not appreciably altered by the administration of pimozide.

In the fourth experiment, the relative reinforcing properties of fencamfamine and cocaine were assessed using a progressive-ratio schedule of reinforcement. Three purebred beagle dogs, with histories of i.v. drug self-administration, were given access to a single response-contingent drug injection during each of three 1-hr. trials per day; these three trials were separated by time-out periods of 3 hrs. The response requirement to obtain one injection each trial was increased daily until the dogs failed to complete the necessary fixed-ratio; i.e., until they reached a "break-point". Several doses of fencamfamine and cocaine (ranging from 0.6-3.0 mg/kg) were tested; drugs were delivered i.v. over 30 sec. The order of testing was randomly determined for each dog and saline was included in the treatment series.

All doses of fencamfamine and cocaine maintained self-administration behavior at FR values considerably above those obtained with saline in all three dogs. In general, there was a positive relationship between dose per injection and FR value completed; that is, with increasing doses of drug, higher "break-points" were obtained. In all three dogs, fencamfamine and cocaine maintained similar behavior; comparable fixed-ratio values were completed with equivalent doses of each drug.

The results of these four experiments indicate fencamfamine and cocaine share many behavioral properties. Both drugs have qualitatively similar effects on schedule-controlled responding; fencamfamine produces cocaine-like discriminative stimuli; fencamfamine, like cocaine, maintains i.v. self-administration behavior, and this behavior is altered by the administration of the dopamine antagonist, pimozide; finally, both fencamfamine and cocaine maintain similar FR values in a progressive ratio paradigm. Thus, fencamfamine appears to be a highly reinforcing drug that may be abused for its cocaine-like effects.

PUPILLARY BEHAVIOR AS A NEURONAL MODEL TO STUDY THE SITE AND MECHANISM OF ACTION OF ADDICTIVE DRUGS

One of the most demonstrative effects of morphine, besides analgesia, is its ability to alter pupillary size-miosis in some species (e.g., dog, monkey, human), but mydriasis in others (e.g., rat, cat). However, little is known about the site or mechanism of action of morphine's pupillary effects. In these studies the paralyzed cat preparation was used to study opiate effects on three components of pupillary activity: size, light reflex, and fluctuation. In this model the animal rests in a sling restraint with a TV camera focused on one eye. All pupillary activities are measured continuously by an infrared video pupillometer connected to a strip chart recorder and a computer.

In a typical experiment baselines of normal pupillary behavior are obtained after dark adaptation for 30 and 60 min; drug is usually administered intravenously at 60 min. The normal pupil in this preparation oscillates at frequencies related mostly to respiratory rate. The fluctuation amplitude is higher during moderate mydriasis than during miosis. At specified intervals a light reflex is obtained by flashing a light and measuring the downward deflection. The typical effects 15 min after i.v. administration of 0.5 mg/kg of morphine 60 min after dark adaptation include: increase in pupillary size, inhibition of fluctuation, and decrease in the amplitude of the light reflex. Naloxone (10-30 μg/kg) antagonizes all three components of morphine's effect.

The mean effect of morphine was determined in six cats in doses of 0.06 to 15 mg/kg i.v. on the three components of pupillary behavior. Morphine produced significant linear dose-related changes in all three parameters. Levorphanol, but not dextrorphan, produced morphine-like pupillary effects, suggesting morphine receptor stereospecificity. Also, the pupillary effects of morphine did not change two weeks following sympathectomy, indicating that sympathetic pathways innervating the iris do not appear to be involved in the pupillary effects of morphine in the cat.

Single experiments that explore the role of released circulating catecholamines in the mechanism of morphine's mydriatic effects in the cat have now been completed. Preliminary results show that after pretreatment with the α-adrenergic blocking agent, phentolamine, morphine-induced mydriasis was partially antagonized, suggesting that at least part of morphine's mydriatic activity may be due to increased catecholamine release. Mydriasis occurred when 10 nmol of normorphine was microinjected into the Edinger-Westphal nucleus of the rostral midbrain. This suggests a possible central site of action for morphine mydriasis involving the preganglionic parasympathetic neurons. Saline injected into the Edinger-Westphal nucleus had no effect.

To further explore the site of morphine's mydriatic action, the effect of loperamide, 0.5 mg/kg i.v. was studied. This anti-diarrheal compound does not cross the blood-brain barrier well, but does have opiate properties in in vitro preparations. Loperamide produced mydriasis, but with a much shorter duration of action than the same dose of morphine. However, unlike morphine, loperamide was completely antagonized by the α-adrenolytic, phentolamine. After pretreatment with both loperamide and phentolamine, morphine was still able to produce a mydriatic effect. This preliminary data is consistent with part of morphine's mydriatic action being indirect, that is to increase the release of peripheral catecholamines which in turn act on the smooth muscle of the iris, and part of morphine's action being central. Experiments are currently underway studying the effects of various prototypic opioids to explore the possible opioid receptor interactions involved in opiate pupillary effects.

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Progress Report From the NIDA Addiction Research Center Baltimore, Maryland (1984)

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During the past year, the clinical pharmacology research ward was closed from April to September, 1983. During this time, the ward was physically remodeled, and a computer system was installed to permit the direct entry of subject and observer data via terminals to the central processor (PDP-11). Despite the shutdown, several studies were initiated and some of the results of these completed or partially completed studies will be presented in this report.

INVESTIGATION OF COMPULSIVE BEHAVIORS

Within recent years, there has been an increasing acceptance of the concept that common mechanisms underlie the compulsive use of a variety of substances. This concept follows from the observations that most substances of abuse serve as positive reinforcers, and act as euphoriants in post-addict subjects. In addition, most substance abusers abuse several drugs, often from different pharmacologic classes. The following two studies were conducted to determine whether or not a non-drug controlled compulsive behavior showed similar mechanisms with drug abuse. The strategies used were based on those developed over the years at the Addiction Research Center to study prototypic drugs of abuse (Jasinski, Johnson and Henningfield, 1984).

Pathological Gambling

Winning at compulsive gambling has been compared to drug abuse since the behavior may become compulsive, winning is exceedingly reinforcing, and the gamblers self-report a drug-like euphoria state looked on as a positive reinforcer. In the present experiment nineteen volunteers with histories of compulsive gambling were asked to simulate winning at gambling. This was done to learn if an euphoric response accompanied winning, similar to that produced by substances of abuse. In these studies, outpatient subjects were given a series of psychometric tests. This included an extensive drug history questionnaire which was modified to include a history of gambling. Then, on two separate occasions,

they were administered the Addiction Research Center Inventory (ARCI). One time they were asked to complete the ARCI as they felt that day and on the other, they were asked to complete the ARCI as they felt when they were winning at gambling. The use of simulated tests has been shown to be a valid measure of euphoric responses to drugs.

Of particular interest was the observation that the mean score for the compulsive gamblers on the Psychopathy Scale of the MMPI was 63.26. This compares with the mean score in normals of 43.62 and in the addict population of 68.21. The profile of responses on the ARCI indicated that winning at gambling produced significant responses on the Morphine Benzedrine Group (MBG), simulated opiates, popularity, efficiency and Benzedrine Group Scales. This profile is most similar to that produced by amphetamine and opiates. Opiates, however, do not produce significant responses on the Efficiency and Benzedrine Group Scale.

Overall, this clinical assessment of gambling indicated there were some commonalities between gambling and drug abuse.. First, there are positive early experiences associated with winning, elevated psychopathy score, and within the subcultural areas enhanced social status associated with winning. More importantly, the winning is associated with an euphoric response as measured by elevated MBG scale scores, a measure of drug-induced euphoria.

Abuse Liability of Glucose

These studies were done in four volunteers who had histories of substance abuse. The purpose of these studies was to learn if glucose given intravenously was an euphoriant. Our interest was to learn if glucose ingestion compared with the model for compulsive behavior. A secondary purpose was to provide controls for our studies on cerebral metabolism using rate of glucose turnover as measured in Positron Emission Tomography.

In these studies, subjects were given 10, 20, and 40 mg of glucose and saline, each infused over three minutes after a 12-hour fast. Experimental procedures and the measures were those developed for measuring the effects of intravenous boluses of nicotine. The subjective behavior and physiologic measures were taken every 12 seconds, five minutes before, during, and after the infusion.

The glucose infusions were discriminated from saline infusions; however, there was no alteration in mood. The effects of the glucose infusions were disliked because of pain at the infusion site. Infusions of glucose were physiologically active, since pupil diameter, skin temperature and heart rate, and arm EMG all increased. From these experiments we conclude that under conditions and in populations where substances of abuse are psychoactive and euphoriants, glucose did not produce euphoria.

AVERSIVE EFFECTS OF NICOTINE

One of our recent areas of investigation has been to investigate relations between subjective effects and drug taking in operant paradigms. Previously, we reported that euphoric and positive reinforcing effects of nicotine were complexly related. Subjective euphoria and reinforcing efficacy are both directly related to dose; however, over the course of a test session, tolerance develops to the euphoric effects of the drug, whereas preference for the drug over nicotine is unchanged. In the presently reported study, the relationship between the aversive properties of nicotine and subjective dysphoria were similarly studied. During three-hour sessions, pressing one lever produced nicotine injections and pressing the other lever blocked the presentation of programmed injection. The subjects were three volunteers who had failed to self-administer nicotine in excess of placebo (saline).

The experimental paradigm is similar to that described previously for self-administration of nicotine. Fifteen minutes before each three-hour test session, a subject was given a single dose of the drug which was to be presented during the subsequent test session. One minute after the injection was given, the subject marked the degree of any positive (euphoric) effects and the degree of any negative (dysphoric) effects on positive and negative visual line analogue scales, respectively. During the subsequent test session, injections were programmed to occur at either 15-or 30-minute intervals. By pressing one lever 10 times prior to the scheduled injection, the stimulus lights were extinguished and the dose was not delivered. At the start of the next day trial (15 or 30 minutes before injection), the stimulus lights were again turned on.

Subjective effects and operant avoidance behavior generally covaried. The number of injections avoided was directly related to drug dose in each of the three subjects tested. Similarly, scores on the negative visual line analogue scale were somewhat more sensitive to drug dose manipulations and were directly related to dose level.

INVESTIGATION OF OPIOID SUBCLASSES

Studies of the opioids, cyclazocine, and nalorphine in the chronic spinal dog, in conjunction with human studies, suggested that the effects of these drugs were mediated through receptors other than the mu-type thought to mediate the effects of morphine (Gilbert and Martin, 1976; Martin et al., 1976, Jasinski et al., 1970). Martin proposed that ketocyclazocine represented a prototype of one subclass of opioids which act through stimulation of receptors which he labeled "kappa". We conducted studies to learn if the pharmacologic profiles of morphine, ketocyclazocine, and cyclazocine differed. We wished to know whether abstinent drug abusers could discriminate among these three drugs. The design of the study also included the administration of large doses of naloxone to determine if naloxone is pharmacologically active. Our original studies with naloxone revealed little pharmacologic activity at

doses up to 30 mg (Jasinski, Martin, Haertzen, 1967). However, in recent years, larger doses of naloxone have been used in clinical and research medicine. The effects of these doses have been attributed to antagonism of endogenous opioid substances.

Data are presented from the first five subjects who have completed the study protocol. The measures included standard measures for assessing the effects of single doses of substances of abuse. They are the Single Dose Questionnaire for subjects and observers, the full Addiction Research Center Inventory (ARCI) and selected subscales, the Morphine Benzedrine Group (MBG), LSD and Pentobarbital-Chlorpromazine Alcohol Group (PCAG) scales. The physiologic measures included blood pressure, pulse, temperature, and respiratory rate.

Some new psychometric measures were developed for inclusion in this study. One is a scale which calls for a categorical-numerical rating of 0, 1, 2, 3, or 4 in response to the question, "How much do you feel the medicine?" Beside the "0" response, the word "none" is written and beside the "4" response the word "maximum" is written. No other prompt words appear, allowing the subjects to scale the intensity of the feeling state.

The initial studies of ketocyclazocine prompted the development of another scale, the Perception Scale, based on questionnaires developed by Abramson and Isbell (Isbell et al., 1956) which are useful for measuring the effects of LSD and hallucinogens. There are 40 questions which reflect alterations in the five senses, cognition, feelings of detachment, paranoia, and general mood. The subject is confined to 10 categorical-numerical responses, the digits 0-9, which represent the intensity of the particular feeling state. The full questionnaire is scored by summing the numerical responses. The scale is also broken down into subscales which group questions probing one sense or mental process. These subscales are scored individually.

Lastly, a drug discrimination procedure was introduced which called for the subject to identify the drug 24 hrs after administration. This was done by conducting the study in two parts, training and discrimination. The training part consisted of giving intramuscular injections of morphine, 21 mg, ketocyclazocine, 0.85 mg, cyclazocine, 0.7 mg, naloxone, 210 mg, and placebo in random order identifying them only as A, B, C, D, and E. Subsequently, in the discrimination phase, the subjects receive morphine, 15 and 30 mg, ketocyclazocine, 0.6 and 1.2 mg, cyclazocine 0.5 and 1.0 mg, naloxone, 150 and 300 mg, and placebo given in random order under double-blind conditions. Twenty-four hours later the subjects are asked to identify the unknown drug by writing the letter code from the training phase which matches the unknown drug.

Further investigation was conducted into biochemical markers of kappa and mu activity. Kappa agonists appear to inhibit ADH release resulting in increased urine production while morphine, a mu agonist, increases ADH release and decreases urine volume

(Nutt and Jasinski, 1974). During the training phase of the experiment, plasma and urine were collected for ADH assay and urine for determination volume and osmolarity per unit time. Preliminary results indicate that morphine decreases urine output and ketocyclazocine increases it.

RESULTS

The onset of action of ketocyclazocine is more rapid than cyclazocine or morphine. The activity of ketocyclazocine is apparent at 15 minutes after administration and peaks at 30 minutes, declining rapidly thereafter to baseline by three hours. Morphine and cyclazocine did not reach peak activities until one hour after administration and their effects were still present at 8 to twelve hours.

Among the physiologic responses, morphine and cyclazocine caused an increase in the supine systolic blood pressure, temperature depression, and miosis. Only morphine caused a depression in the respiratory rate. Ketocyclazocine caused an increase in the supine systolic blood pressure and a decline in body temperature was detected at the high dose only. Apart from these, it had no other activity among these measures. The absence of miosis clearly differentiated ketocyclazocine from cyclazocine and morphine.

The drug discrimination procedure of drug identification by letter code demonstrated that the subjects could distinguish among the five drugs that were administered. The results of the chi square analysis rejected the null hypothesis of chance arrangement of drug identifications with a p value much less than 0.05. The subjects correctly identified the drugs 29 times out of 45 trials (65%). Among the drug identification errors, ketocyclazocine was cross-identified with cyclazocine six times but was not confused with morphine. In contrast, cyclazocine was confused with placebo, morphine, ketocyclazocine, and naloxone.

Morphine was significantly different from the placebo on the "Feel the Drug, Opiate Symptoms, Subject's Liking and MBG" scales. It had no effects on the PCAG and LSD scales. Cyclazocine and ketocyclazocine however, produced responses different from placebo on the "Feel the Drug and LSD" scales with no significant responses on the "Opiate Symptoms, Subject's liking, MBG or PCAG" scales. Thus, the pattern of responses of ketocyclazocine and cyclazocine was identical. Analysis of the Perception Scale indicated that morphine affected only the subscale relating to tactile responses. Ketocyclazocine produced a striking response on the full scale and had activity on the subscales of general effect, detachment, auditory, tactile, dizziness, cognition, and paranoia. Exceptions to its activity are the smell, visual, and taste subscales. Cyclazocine also demonstrated significant activities on the full Perception Scale at low and high doses. It had activity on the general, detachment, tactile, dizziness and cognition scales but only at the high dose. We conclude that cyclazocine is like ketocyclazocine in its profile of subjective effects, especially

at high doses; however, it is not identical to it. Morphine is very different from ketocyclazocine. This is most clearly distinguished by the profile of subjective effects. The profile of physiologic effects less clearly discriminates among morphine, ketocyclazocine and cyclazocine but important differences were observed. The most important distinguishing physiologic measure was pupil response in that it demonstrated that ketocyclazocine was different than both morphine and cyclazocine.

Naloxone was pharmacologically active in these subjects at the very large doses given in this study. The onset of effects was noted at the 30-minute post-drug observation for the group. The drug effects did not reach peak activity until one to two hours, gradually resolving by about eight hours. The activity did not appear dose-related because the peak effects and duration did not change as a function of increasing dose. Naloxone caused few changes in the subjective measures. It was significantly different from placebo on the "Feel the Drug" scale. The full "Perception Scale" measured differences between naloxone and placebo only for the low dose. There were trends for significant responses on the general and detachment subscales. There were also some trends on the "Opiate Symptoms Scales." The full scale, the "yawning", and "high" symptoms all trended toward significance with five subjects completed in the study. Naloxone did not constrict pupils; however, the systolic blood pressure (supine and standing) increased and body temperature was depressed compared to placebo.

Thus, it is demonstrated that naloxone is a pressor in the absence of hypotension. There was a trend for respiratory depression and an increased pulse rate. On the basis of these studies, it is concluded that naloxone is pharmacologically active at doses of 150 and 300 mg when compared to placebo on both phsyiologic and subjective measures. The profile and time course of effects resemble a weak agonist rather than precipitated abstinence, though the study is incomplete.

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Progress Report From The Division of Behavioral Biology, The Johns Hopkins University School of Medicine

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The Division of Behavioral Biology is the site of a group of multifaceted research projects dealing with the behavioral pharmacology of substance abuse. The general aim of this program of research is to promote a fuller understanding of addictive disorders and of their behavioral and biomedical foundations; in particular, the laboratory focuses upon determinants of drug self-administration and determinants of adverse drug effects. This aim is pursued via systematic experimental study of the contributory deterministic roles both of behavioral and of pharmacological factors.

The range of research in the Division is illustrated in the outline in Table 1. A major program of preclinical behavioral pharmacology research is conducted within the animal laboratories at the Medical School campus; in addition, a large clinical research program is conducted, primarily on the campus of the Francis Scott Key Medical Center. In both the animal and human laboratory settings research focuses upon a similar array of substance abuse related issues -- analysis of drug self-administration behavior, evaluation of drug stimulus characteristics via operant drug discrimination procedures, and assessment of the behavioral and biomedical consequences or sequelae of drug intake. In addition to these experimental laboratory settings, the Division conducts related research in various applied settings. These applied settings provide the opportunity to examine the relevance outside the laboratory of principles and relationships observed in the laboratory, and they provide the opportunity to conduct controlled clinical trials of treatment interventions for substance abuse problems.

This progress report will summarize the Division's work in these areas over the past year.

TABLE 1. Outline of Research Program and Settings

I. PRECLINICAL BEHAVIORAL PHARMACOLOGY

1. Drug Self-Administration
2. Drug Discrimination
3. Assessment of Drug Effects

II. CLINICAL BEHAVIORAL PHARMACOLOGY

A. Laboratory Settings

1. Drug Self-Administration
2. Drug Discrimination
3. Assessment of Drug Effects

B. Applied Settings

1. Drug Self-Administration
2. Assessment of Drug Effects
3. Treatment Intervention Trials

I. PRECLINICAL BEHAVIORAL PHARMACOLOGY

A. SELF-ADMINISTRATION

In the primate laboratory an experiment by Lukas, Griffiths and Brady has examined the self-administration of a range of doses of eight different opioid compounds. A substitution procedure was used, in which baboons outfitted with intravenous catheters were initially trained to self-administer cocaine (0.32 mg/kg/inj); following stabilization of the cocaine performance an opioid test dose was substituted for the cocaine for 12 - 15 days. The stable cocaine performance was re-established prior to each test dose substitution. Thus, these evaluations of opioid reinforcing efficacy were conducted in subjects who were not opioid dependent. Single injections were available once every three hours, so the maximum possible was 8 self-injections per day.

The two agonists codeine and morphine and the three mixed agonist-antagonists butorphanol, nalbuphine and pentazocine all showed parallel ascending dose effect curves, but with morphine showing a lower peak. Neither SKF 10,047 nor naloxone were self-administered above vehicle levels. Self-administration of buprenorphine occurred in only one of three animals, and showed a very shallow dose-effect curve.

It is of interest that morphine, which is recognized as a compound of high abuse liability, maintained lower peak self-administration than codeine, butorphanol, nalbuphine or pentazocine -- all of which are considered to be of lower abuse liability. Unfortunately we are not able to explain the basis for this finding, but two possibilities are: first, that morphine's reinforcing efficacy may be lower in the absence of physical

dependence; or second, that morphine self-administration may be suppressed by morphine's relatively greater potency in disrupting operant behavior.

B. DRUG DISCRIMINATION

A second major area of activity within the animal laboratory has been the use of the drug discrimination methodology to assess the similarities and differences in the stimulus properties of various compounds. In the drug discrimination procedure animals are trained to make one operant response after having received a specific training drug and to make a different operant response after having received vehicle only. The response made after receipt of test doses provides information concerning the stimulus similarity of the test compound to the training compound.

Work by Ator, Griffiths, and Brady has examined the stimulus generalization of a range of novel anxiolytics to standard training drugs. Each of the test drugs was studied over a range of doses. The results are summarized in Table 2. A "plus" mark indicates the test drug showed stimulus generalization -- or stimulus similarity -- to the training drug; a "minus" mark indicates it did not; a blank indicates that particular condition was not tested.

TABLE 2. Drug Discrimination Cross Generalization

	Training Drug			
	Lorazepam		Pentobarbital	
Test Drug	Baboon	Rat	Baboon	Rat
Pentobarbital	-	-	+	+
Lorazepam	+	+	+	+
Triazolam	+	+	+	+
Zopiclone	+	+		+
CL 218,872	+	+		+
Buspirone	-	-		-
CGS 9896	-	-	-	-
PK 9084	-	-		-

Subjects were trained either in a lorazepam versus no drug discrimination or in a pentobarbital versus no drug discrimination. Both baboons and rats were trained in each discrimination. It should be noted that there is cross-species generality in all the conditions where it was tested.

An assymmetry was observed in the pentobarbital-lorazepam discrimination. While both pentobarbital and lorazepam were discriminated as being similar to pentobarbital, only lorazepam was discriminated as being lorazepam-like; pentobarbital was not. This assymmetry was replicated across species.

Triazolam, a hypnotic benzodiazepine, showed a stimulus characteristic profile similar to that of the anxiolytic benzodiazepine lorazepam, not like that of the hypnotic pentobarbital.

The remaining compounds in the table are all novel anxiolytics with non-benzodiazepine structures. Despite their non-benzodiazepine structures both zopiclone and CL 218,872 show a profile of discriminative stimulus characteristics similar to the benzodiazepines. Other data have indicated that these compounds have anti-conflict or anxiolytic activity, and that they show benzodiazepine binding.

The bottom two compounds -- CGS 9896 and PK 9084 -- are quinoline derivatives that also show benzodiazepine binding and show anxiolytic-like anti-conflict activity in preclinical studies. However, neither of these was discriminated as having benzodiazepine-like stimulus properties.

The final compound -- buspirone -- is a piperazinyl derivative which does not show benzodiazepine binding but which is reported to have anxiolytic activity. It was not discriminated as being either lorazepam-like or pentobarbital-like.

C. ASSESSMENT OF DRUG EFFECTS

A third activity in the animal laboratories has involved assessment of the behavioral consequences of drug intake -- i.e., characterization of drug-produced performance disruptions. The primary procedure being used is that of assessing the psychophysical thresholds and reaction times for stimulus discrimination in baboons. This is done by training animals to make specific operant responses when they detect a stimulus, and then assessing the sensitivity and speed of their performance following test dose administration.

During this year Lukas, Hienz, and Brady have completed a comparative evaluation of diazepam and triazolam using this psychophysics procedure. Diazepam produced dose-related elevations of both auditory and visual thresholds and reaction times. In general, triazolam produced similar effects (except it did not elevate auditory threshold), and it was approximately 100 times as potent as diazepam.

There were marked differences in the time course of the sensorimotor impairments produced by the two drugs -- presumably the result of long-acting metabolites following diazepam and not triazolam. Following single high doses of diazepam, impairment was detectable for up to 4 - 5 days. There was no residual day-after effect following triazolam.

II. CLINICAL BEHAVIORAL PHARMACOLOGY

A. LABORATORY STUDIES

1. Self-Administration

A drug self-administration methodology in the form of a behavioral choice procedure is one of the bases of the laboratory's clinical drug abuse liability testing program. In this procedure subjects are given scheduled exposures to test compounds and are subsequently permitted to choose which of those they prefer next to receive. Use of the drug self-administration choice procedure in clinical drug abuse liability assessments is illustrated in a paper by Griffiths and colleagues reported elsewhere in this volume. That report compares the reinforcing efficacies of diazepam and oxazepam. Choice comparisons were conducted between placebo and a range of doses of both diazepam and oxazepam as well as between the two active drugs themselves. At comparably sedating doses greater self-administration preference was maintained by diazepam.

A second area of application of the clinical drug self-administration methodology has been in study of the determinants of tobacco smoking. A series of studies have investigated the effects of various drug pretreatments upon smoking. Chait and Griffiths have studied the effects of various methadone doses on cigarette smoking among methadone maintenance patients who participated in 2-hour smoking sessions after receiving either placebo, dextromethorphan (as a taste blind) or one-half, one or two times their usual methadone maintenance dose. Increasing doses of methadone produced increases in various indices of smoking -- including both behavioral measures and biological measures of smoke absorption. This is the most recent in a series of studies which have found cigarette smoking to be increased by a range of drugs of abuse, including d-amphetamine, ethanol, pentobarbital, and now methadone. In contrast, studies of caffeine indicate that it does not affect smoking.

2. Drug Discrimination

During this year Preston, Bigelow, and Liebson have developed and used with human subjects an operant drug discrimination procedure. Opioid-dependent methadone maintenance subjects were trained in a three-way drug discrimination between hydromorphone, naloxone, and saline which were identified to them only by letter codes; subjects were subsequently tested with a range of doses of the two active compounds to assess their stimulus similarity to the training doses. Results showed that the three-way drug discrimination was rapidly learned and resulted in orderly dose effect relations. This human opioid drug discrimination procedure appears promising for the clinical study of the opioid mixed agonist-antagonists. This study is described in greater detail in a separate report in this volune.

3. Assessment of Drug Effects

A number of years ago the Committee awarded this laboratory preliminary funds to develop clinical procedures for assessment of abuse liability. The major procedure used in these evaluations is assessment of the profile and time course of subjective and behavioral effects of test compounds in experienced abusers. Elsewhere in this volume two papers are presented which illustrate the laboratory's application of these procedures to assessing the abuse liability of benzodiazepines.

Griffiths and colleagues describe a comparative evaluation of diazepam and oxazepam over a range of doses in experienced sedative abusers. Figure 1 illustrates the time course of effects on psychomotor performance. Interestingly, oxazepam, which is pharmacokinetically the shorter acting of the two, had a much slower onset and consequently a more protracted time course of acute behavioral effects. Roache and colleagues report a comparison of the benzodiazepine hypnotic triazolam with pentobarbital, also with sedative abuser subjects. On the day following drug administration subjects provided estimates of the dollar value of the test dose. Interestingly, at dose ranges that produced similar effects for both drugs on objective indices of sedation and intoxication, subjects' subjective evaluations of triazolam's reinforcing value were much lower than for pentobarbital.

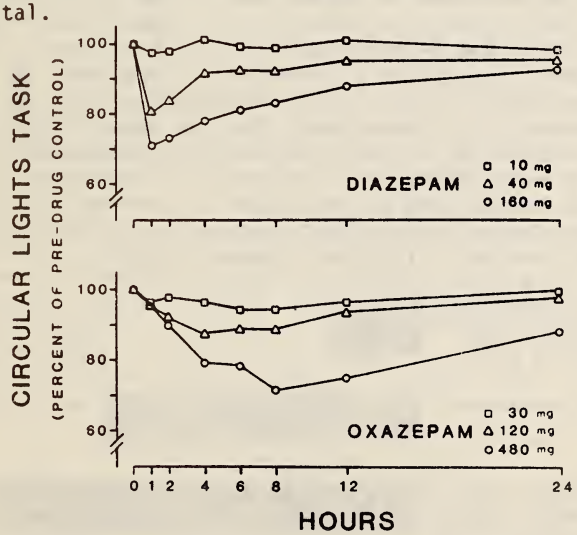

FIGURE 1. The time course of behavioral disruption following oral administration of a range of doses of diazepam or oxazepam to sedative abuser subjects is shown. In this performance task subjects responded by touching randomly illuminated lights in a circular array.

B. APPLIED SETTINGS

1. Self-Administration

Studies in applied settings allow one to assess whether relationships and principles observed in laboratory studies have generalizable practical relevance in clinical settings, and they allow one to assess whether there may be factors acting in clinical settings which are being overlooked in laboratory studies.

For some time this laboratory has been interested in whether the construct of a drug's reinforcing efficacy or abuse liability is related to the extent of the drug's self-administration by normal patients in therapeutic contexts or whether this construct relates more narrowly to the behavior of the somewhat deviant population that engages in illicit drug abuse. Bigelow and Liebson have been examining the self-administration of the phenylethylamine anorectic-stimulant drugs using a behavioral choice procedure in a therapeutic weight control clinic population. In these studies overweight patients are exposed for one week durations to each of two alternative drugs and are then allowed to choose the drug which they will next receive. There is a one-week washout between drug exposures and the cycle repeats for multiple choice exposures for each subject. Figure 2 summarizes the results of three experiments, each of which compared one of the phenylethylamines to placebo. Diethylpropion, which has an amphetamine-like profile of effects, maintains drug preference well above placebo levels; chlorphentermine, which has a profile of effects that is more fenfluramine-like, suppresses drug preference well below placebo levels (interestingly, chlorphentermine has been discontinued from production because of poor sales); phenylpropanolamine, the active ingredient in over-the-counter diet aids, was not distinguished from placebo. These data on preference in this applied clinical setting are compatible with laboratory data concerning the relative reinforcing efficacies of these drugs.

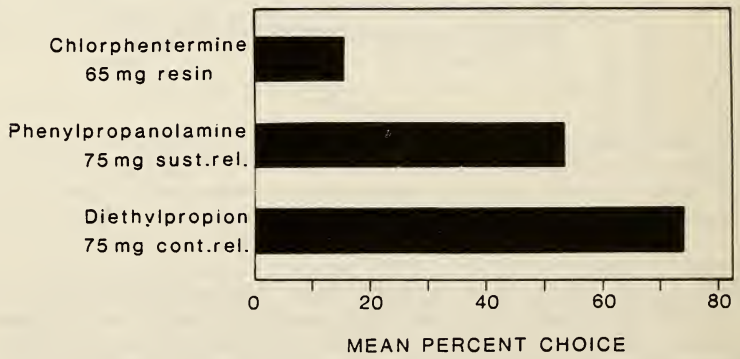

FIGURE 2. Mean percent choice for active drug versus placebo by weight control outpatients is shown. In three separate experiments placebo was compared to each of three phenylethylamine anorectics.

A second applied setting in which drug self-administration is studied is the methadone maintenance clinic. A study by Stitzer and colleagues has used a behavioral choice drug self-administration procedure to assess the reinforcing efficacy of acute increases in the methadone dose. In this study patients were offered, in a mixed order, the opportunity to choose between various size methadone dose supplements and financial payments of either $1 or $5. The percent of dose supplements chosen was examined as a function of dose magnitude and as a function of magnitude of the financial alternative. Graded dose-effect relations were observed, with larger doses maintaining greater drug preference, and the curve was shifted to the right by increasing the magnitude of the financial alternative. The demonstration that acute methadone dose supplements function as reinforcers suggests the utility of incorporating such changes into contingent reinforcement behavioral interventions for the promotion of therapeutic changes.

2. Assessment of Drug Effects

When patients enter methadone treatment one would like to dispense a dose of methadone which is sufficient to suppress the opioid abstinence syndrome but which is not so great as to produce acute behavioral intoxication or behavioral impairment in its own right. Unfortunately no adequate procedure has been available for rapid determination of the degree of opioid tolerance with which addicts present. A recent study by Higgins and Stitzer has evaluated the utility of an acute oral methadone challenge as a technique for assessing degree of opioid tolerance. Participants were heroin addicts applying for outpatient methadone detoxification; at intake they were given a standard dose of 20 mg methadone orally and were assessed over the course of 2 hours. Figure 3 shows the relationship between the magnitude of their heroin habit -- measured in dollars per week reportedly spent for heroin -- and the change in pupillary diameter constriction produced by the methadone challenge. The correlation between the two was highly significant, with $r = -0.65$. Thus, this methadone challenge procedure appears to be a simple and effective technique for estimating degree of opioid tolerance. A future prospective clinical trial will assess whether tolerance levels at admission are predictive of success in treatment.

3. Treatment Intervention Trials

One of the important aspects of drug dependence research which can only be conducted in applied settings is, of course, the conduct of therapeutic intervention trials. This has been one of the major functions served by this laboratory's outpatient methadone treatment research clinic. The results of three such treatment intervention trials are reported separately elsewhere in this volume. Stitzer and colleagues report the effects of methadone dosage manipulations during detoxification. Higgins and

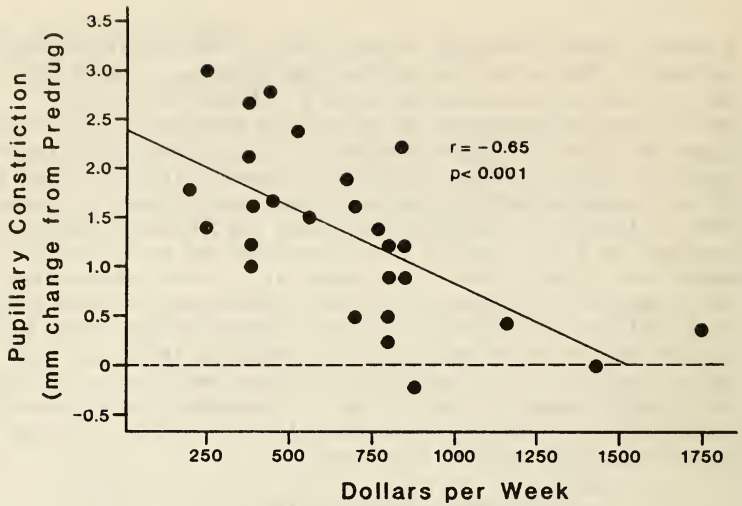

FIGURE 3. Magnitude of pupillary constriction in response to an oral 20 mg methadone challenge is shown as a function of dollars per week reported spent for illicit heroin. Subjects were outpatient applicants for methadone treatment.

colleagues report the effects of using methadone dose alterations as behaviorally-contingent reinforcers to encourage abstinence from illicit drugs during detoxification. McCaul and colleagues report on the comparative effects of diazepam and doxepin when used as pharmacological adjuncts to methadone detoxification. These studies will not be described here.

A final setting in which therapeutic intervention trials have been conducted is in medical settings where patients with substance abuse problems are seen for routine medical care. This is an especially appropriate setting for studies of tobacco dependence given its strong association with a wide variety of health problems. Bigelow and Burling recently conducted a randomized antismoking intervention trial among pregnant smokers attending a hospital-based prenatal clinic. Women were randomized between a usual care condition and a special intervention condition which received a strong directive antismoking letter mailed to their home from the clinic director. Results are shown in Figure 4; the letter intervention produced a statistically significant increase in smoking abstinence which was detectable at subsequent clinic visits for up to ten weeks.

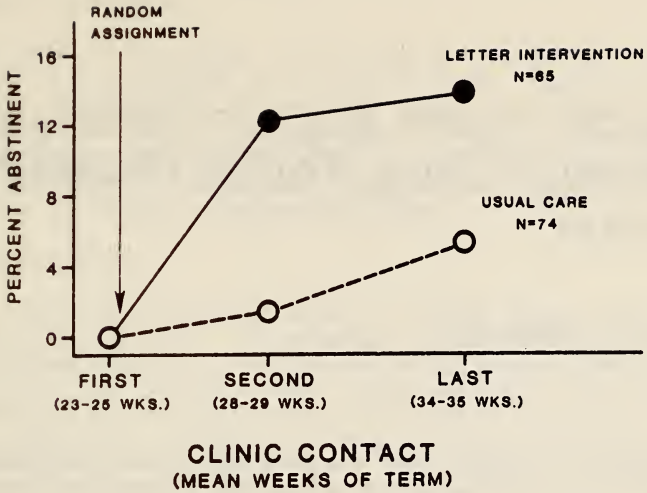

FIGURE 4. Percent of patients abstinent from smoking is shown as a function of treatment condition over successive clinic contacts. Patients were pregnant women smokers attending an outpatient prenatal clinic.

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Report From The University of Chicago Drug Abuse Research Center

Chris E. Johanson

Researchers associated with the Drug Abuse Research Center at the University of Chicago have been investigating the biological and behavioral mechanisms underlying the reinforcing properties of anorectics for several years. Our evaluation of anorectic drugs includes measures of their efficacy as anorectics as well as their neurotoxicity to complement the assessment of dependence potential. We have expanded our evaluation by using comparable procedures across species, including humans. The goal of this research program is to develop and validate procedures which can be utilized to develop safe anorectic agents with lower dependence potential than those currently available. Even more recently we have expanded our investigations to include anxiolytic drugs with the same purpose. Because of our interests and background, we were asked to participate in developing CPDD's screening effort for anorectic and anxiolytic drugs. This report includes a review of previous work as well as preliminary results on compounds evaluated specifically for CPDD.

The procedures typically used for compounds suspected or known to be anorectic-like include measures of anorectic properties (food intake in both rats and monkeys), drug discrimination with subjects (pigeons, monkeys, and humans) trained to discriminate amphetamine from placebo, and drug self-administration in monkeys and humans. Measures of neurotoxicity of repeated dosing in rats are included when possible. Similar types of studies are done with anxiolytics but to date we have only implemented drug discrimination studies in pigeons and monkeys and self-administration studies in monkeys and humans. For procedures where different species are used, an effort is made to have the protocols as similar as feasible.

The use of multiple measures of drug action allows several kinds of comparisons to be made which, when viewed as a whole, can aid in a cost-benefit analysis of a compound. For instance, if the ED_{50} for decreased food consumption is considerably lower than its ED_{50} for discrimination, patients receiving the medication may not ever experience any subjective effects which increase the likelihood of dependence potential. In contrast, the opposite relationship is less desirable.

ANORECTIC DRUGS

For purposes of illustrating our approach for anorectics, I will review a series of animal studies on 7 anorectic drugs. Results with humans will not be included. These drugs include d-amphetamine (AMP), phenmetrazine (PM), diethylpropion (DEP), mazindol (MZ), methylphenidate (MP), fenfluramine (FF), and phenylpropanolamine (PPA). These were selected because they include drugs with varying dependence potential and varying neurochemical effects.

Anorectic Efficacy

Rats were given 15 minutes access to a milk solution each day and their intake measured. Dose-response functions were obtained by administering drugs (S.C.) 15 mins prior to the session. Rhesus monkeys were given 2-hr access to food pellets each day and their intake measured. Drugs were given intragastrically 60 mins prior to the session. Using ED_{50}'s for comparison, the rank ordering of potencies in both rats and monkeys was: AMP MZ FF DEP PM MP. These potencies correspond to the therapeutic dose. However, for PPA, there was a marked difference in the efficacy and potency in the two species. In rats, PPA had no effect in doses up to 128 mg/kg, whereas in the monkey PPA was both a potent and efficacious anorectic. Our failure to decrease food intake in the rat is in contrast to studies by Kornblith and Hoebel (1976) in which doses of 5, 10 and 20 mg/kg of PPA produced a significant decrease in food intake in rats. Further research is necessary to determine what variables account for these differences.

Neurotoxicity

For the past 10 years we have worked in association with Dr. L. Seiden to investigate the possible neurotoxicity of various anorectic drugs. Amphetamines produce damage to DA neurons in several species which strongly suggests that such changes would also occur in humans. What is not known is whether the amphetamines are unique in this regard or whether other anorectic drugs produce similar effects.

A major problem in comparing drugs for their possible neurotoxic effect is the selection of appropriate doses. The data on anorectic potency in rats allowed the calculation of an ED_{50} dose for each drug which could be used as the point of comparison for the selection of doses to be tested for neurotoxicity. Generally, doses of 5, 10 and 20 times the ED_{50} for suppression of food intake were selected for investigation, although higher or lower doses might be tested if necessary. Half of each daily drug dose was administered subcutaneously in two divided doses at 0700 and 1700 hours for 4 consecutive days to a group of male rats. Control rats were injected with the drug vehicle. Two weeks after completing the 4-day treatment period, rats that survived the drug regimen were killed for monoamine level determinations in specific areas.

There were marked differences in the effects obtained with the various anorectic agents. AMP produced a decrease in the levels of DA and 5HT in certain regions of the brain including the striatum and

hippocampus but had no effects on NE in any area. The minimal dose (25 mg/kg) required to produce this effect was 20 times the ED_{50} dose for suppressing milk intake. On the other hand, MP produced no effects on the levels of DA, NE or 5HT at doses up to 5 times (50 mg/kg) its ED_{50} for anorexia. Higher doses could not be evaluated because they were lethal. MZ at a dose 40 times (120 mg/kg) its ED_{50} for anorexia produced a small but significant decrease in NE levels in the hippocampus and rest of brain. DEP at a dose 10 times (100 mg/kg) its ED_{50} for anorexia produced a decrease in serotonin levels in the hippocampus and rest of brain. FF also produced a long lasting depletion of serotonin in the striatum, hippocampus and rest of brain at a dose (6.25 mg/kg) only 1.25 times the ED_{50} dose for anorexia. In the case of the other anorectics, the minimal dose necessary to produce a prolonged neurochemical effect varied from 10 (DEP) to 40 (MZ) times the ED_{50} dose. It would thus appear the fenfluramine is a significantly more toxic drug than the other anorectics tested.

Drug Discrimination

The same compounds were evaluated in the drug discrimination paradigm in pigeons trained to discriminate between 2 mg/kg (i.m.) AMP and saline in a two-lever food-reinforced procedure and in monkeys trained to discriminate 1 mg/kg (i.g.) AMP from saline in a two-lever shock avoidance procedure. During test sessions, five of the anorectics substituted for AMP in a dose-dependent manner in both species. For pigeons the order of potency was MZ AMP = MP = PM DEP. In monkeys the order of potency was: AMP PM MZ DEP MP. In pigeons PPA also substituted but was the least potent. However, only 1 of 3 monkeys, at a dose of 100 mg/kg, responded on the drug-appropriate lever. There was partial substitution of FF in pigeons but none in monkeys.

Self-Administration

Rhesus monkeys have been used extensively to assess the dependence potential of new compounds (Johanson and Schuster 1981). In general drugs which are abused by humans are self-administered by monkeys (Johanson and Balster 1978) and those which are not abused do not maintain responding in monkeys. This concordance has led to the acceptance of the self-administration paradigm as an animal model of drug dependence (Thompson and Unna 1977). The dependence potential of the anorectics reviewed in this paper has been evaluated extensively both in our own laboratory as well as others.

Several studies have demonstrated that AMP maintains responding in several species and under a variety of conditions (see Johanson and Schuster 1981). This is also true for MP (e.g., Wilson et al. 1971; Johanson and Schuster 1975), PM (e.g., Wilson et al. 1971; Griffiths et al. 1976; Woolverton, unpublished observations), DEP (e.g., Johanson and Schuster 1977), and MZ (Wilson and Schuster 1976; Woolverton, unpublished observations) but not FF (e.g., Woods and Tessel 1974; Griffiths et al. 1976) or PPA (Woolverton, unpublished observations). These results are in general agreement with the actual levels of abuse

of these drugs and support the use of animal self-adminstration studies as a means of predicting dependence potential.

ANXIOLYTIC DRUGS

Drug discrimination studies similar to those described above have also been done in oxazepam-trained pigeons (i.m. route) and pentobarbital (PB)-trained monkeys (i.g. route). During test sessions, several anxiolytics substituted for the training drug while drugs from other classes (e.g., amphetamine) did not.

In order to evaluate the reinforcing properties of anxiolytics, the standard substitution procedure with cocaine as the baseline drug has not been adequate. For instance, in a study conducted by Bergman and myself, only 3 of 11 monkeys self-administered diazepam. While this may accurately reflect the dependence potential of this drug, it would be difficult to differentiate anxiolytics with less reinforcing efficacy. On the other hand, in that same study it was found that 5 out of 5 monkeys maintained on a PB baseline self-administered diazepam. This had led us to evolve a new strategy for testing the reinforcing properties of anxiolytics. Such drugs are originally tested only in animals with a PB baseline. If responding is maintained, monkeys on a cocaine baseline may be tested.

In previous studies using monkeys on a PB baseline we have shown that midazolam, triazolam, and flurazepam are self-administered by all monkeys tested. Lorazepam and estazolam maintain responding in about 50% of the monkeys whereas enciprazene was not self-administered by any of the monkeys tested.

CPDD COMPOUNDS

We have been sent 6 coded compounds from CPDD, 4 said to be anxiolytics and 2 anorectics. To date these have been tested in drug discrimination and self-administration. All compounds regardless of what information we are given are initially tested in the drug discrimination studies with pigeons, one group trained with amphetamine and a separate group with an anxiolytic. The outcome of these studies determines what further tests are done. If the drug is anorectic-like, further drug discrimination studies are done with amphetamine-trained monkeys and the reinforcing properties are evaluated in monkeys maintained on a cocaine baseline. If, on the other hand, the drug is sedative-like, drug discrimination studies are done in monkeys trained to discriminate PB and the reinforcing properties are evaluated in monkeys maintained on a pentobarbital baseline. If responding is maintained, a drug may be tested using the alternative baseline in additional monkeys.

Anxiolytics

When the studies were completed, the four anxiolytics were revealed to be diazepam, bromazepam, temazepam and halazepam. All four substituted as a discriminative stimulus for oxazepam in pigeons and PB

in monkeys but did not substitute for amphetamine in pigeons. Three of the compounds were similar in potency with halazepam being less potent. All four compounds were self-administered in PB-baseline monkeys. In cocaine-baseline monkeys, a previous study showed that 3 of 11 monkeys self-administered diazepam. The other 3 anxiolytics were tested in 2 cocaine-baseline monkeys. Bromazepam and temazepam were not self-administered but halazepam was.

Anorectics

Only 2 compounds purported to be stimulant-like have been tested and as yet the identity of these compounds is unknown. One of these drugs (CPDD 5) substituted for AMP in both pigeons and monkeys but did not substitute for oxazepam in pigeons. The second compound (CPDD 6) partially substituted for AMP in both species but not for oxazepam in pigeons. CPDD 5 was self-administered in 4 cocaine-baseline monkeys whereas CPDD 6 was not. CPDD 5 was also self-administered by the two PB-baseline monkeys. In one of these monkeys, intake was extremely high and convulsions occurred. When that monkey was returned to the PB baseline, increased sensitivity to its sedative effects were observed. This same monkey also self-administered CPDD 6, tested after CPDD 5, but the second animal did not.

Summary

In summary, I have reviewed the results from 6 coded compounds we have evaluated as part of CPDD's efforts to expand into testing the dependence potential of anorectics and anxiolytics. I have reviewed a great deal of additional studies in order to place the results with the test drugs into a broader context and also to demonstrate our experience in evaluating these classes of drugs. Clearly the 4 anxiolytic drugs were well characterized by our tests. The two compounds designated as anorectics are still unknown to us. CPDD 5 appears amphetamine-like, is self-administered, and in both tests is 1/10th as potent as amphetamine. The results with CPDD 6, however, are less clear. In the drug discrimination studies, it only substitutes for amphetamine in some animals, and in monkeys has minimal reinforcing properties.

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Analgesics 3. Synthesis, Resolution, X-Ray Structure Determination, Receptor Binding, and Analgesic Properties of 3-Methyl-3-m-Hydroxyphenylpiperidines With N-Substituent Variation

Alice C. Cheng; Edward T. Uyeno; Lawrence Toll; Christopher Keys; Dale Spangler; Joseph I. DeGraw; Gilda H. Loew; Arthur Camerman; and Norman Camerman

Phenylpiperidines are an important class of compounds that interact with opioid receptors. (Kugita et al., 1964, Jacoby et al., 1974, Iorio and Casy 1975, Jacoby et al., 1981). Recently, (Lawson, et al., in press) our laboratory has been involved with the synthesis and pharmacological studies of several series of 3- and 4-phenylpiperidines. All these compounds were shown to exhibit mixed analgesic agonist and antagonist activities. Among the compounds studies, the 3-phenylpiperidines possess optical activity. Because of the chirality, the agonist/antagonist potency ratios observed could have resulted from different activities of the enantiomers of the compounds in addition to factors such as binding of different conformations or orientations of the compounds at the receptor. In order to clearly address this issue, the absolute configuration of the chiral center should be taken into consideration. To the best of our knowledge, no reports have appeared in which the actions of optically active 3-(m-OH)phenylpiperidines have been examined for their in vitro receptor binding and in vivo pharmacological activities.

Consideration of the general structural-activity relationship (SAR) requirements of the receptor as well as steric, conformational or stereochemical factors may help to probe the nature of the opiate pharmacophore and its mode of interaction with the opioid receptors. Enantiomeric pairs are particularly useful for such probing because they have identical physical properties and thus, unless they undergo differential metabolism, pharmacological differences may reasonably be attributed to receptor-associated events. (Abdel-Monem et al., 1972, Sullivan et al., 1975). In the present study, we have prepared the optical isomers of a series of N-substituted-e-methyl-e-phenylpiperidine analogs (shown in Table 1) in order to investigate their receptor binding behavior and pharmacological activities.

TABLE 1. Optical isomers of 3-phenylpiperidines

Compound (+) and (-)	R	R'
1	H	OCH$_3$
2	CH$_3$	OH
3	Allyl	OH
4	Cyclopropylmethyl	OH
5	Phenethyl	OH

METHODS AND MATERIALS

1. Chemistry

The synthesis of racemic 3-methyl-3-(m-methoxyphenyl)piperidine (1) follows the procedure of Kugita *et al.*,[1] but with some modification (Lawson *et al.*, in press).

We found that (-)-D-tartaric acid was a convenient resolving agent for the resolution of (±)-1; after three recrystallizations from 95% EtOH, a diastereomeric salt was obtained. The liberated amine, upon conversion to the hydrochloride salt, gave a constant specific rotation. The combined mother liquors containing enriched (-)-1, obtained after resolution of (+)-1, when treated with (+)-L-tartaric acid, led to the isolation of (-)-1, which exhibits an opposite rotation of similar magnitude to (+)-1.

Determination of the optical purity of the enantiomers of 1 was achieved by Mosher's method (Dale *et al.*, 1969). Compound (±)-1 was converted to the diastereomeric amides with optically pure (-)-α-methoxy-α-trifluromethylphenylacetyl chloride. The ^{19}F-NMR spectrum of these diastereomeric amides in $CDCl_3$ displayed two equally intense singlets at δ 9.38 and 8.58 ppm for the two trifluromethyl resonances. The amide generated from (+)-1 displayed a major signal at 8.58 ppm and a minor one at δ 9.38 ppm, while integration of the two peaks showed a ratio of 96 to 4. This, coupled with the specific rotations of two enantiomers establishes that they are equally resolved and suggests that they are nearly optically pure.

Direct N-alkylation of the enantiomers of 1 with the three appropriate alkyl halides yielded the desired N-substituted compounds (m-OCH_3 of 3,4,5) (Lawson, *et al.*, In press). A reductive alkylation, using formaldehyde and sodium cyanoborohydride, was employed in the preparation of the N-methyl analog

(m-OCH_3 of 3,4,5) (Lawson et al., In press). The arylmethyl ethers were cleaved by boron tribromide to give the resolved target compounds (2,3,4,5).

2. Opiate Receptor Binding Assay and Data Analysis

Opiate receptor binding assays were performed essentially as described by Pasternak et al., (1975). Briefly, rat whole brain homogenates were prepared, preincubated at 37°C for 1 hr and resuspended in Tris ph 7.7 at 6.7 mg tissue per ml. Receptor-binding incubations contained 1.8 ml tissue suspension, 0.1 ml labeled ligand (usually 1.0 nM) and unlabeled drugs in a total volume of 2.0 mL. The tubes were incubated in triplicate at 25°C for 45 min prior to filtration.

In the present studies, self- and cross-competition experiments were conducted for 4 labeled ligands, at two different concentrations of labeled ligand. This yields a four-by-four "matrix" of competitive inhibition behavior. For each pair of enantiomers inhibition of all 4 labeled ligands was performed. Data obtained from binding studies were analyzed by a modified version of the program LIGAND (Munson and Rodbard 1980) which predicts the receptor binding affinities and capacities using weighted nonlinear, least squares regression analysis.

In the procedure used, all self- and cross-competition studies involving the four labeled ligands were analyzed together assuming a 1-, 2-, 3-, and 4-site model of receptor binding, and results were compared for statistical significance and other indications of reliability. Inhibition data for each of the 4 enantiomeric pairs of N-substituted-3-methyl-e-(m-OH)phenylpiperidines were then added to the matrix obtained for the labeled and unlabeled ligands, and the data reanalyzed simultaneously for self-consistent receptor binding affinities and capacities. Again, 1-, 2-, 3-, 4-site models for receptor binding were systematically explored.

3. Animal Testing

Analgesic potencies of the chemicals and the reference drug (morphine sulfate) were determined by the mouse writhing test, developed by Koster et al. (1959) and Blumberg et al. (1965). The writhing test was chosen as a measure of analgesic activity since these compounds were suspected of having antagonist activity. The median effective doses (ED_{50}) were derived from the dose-response curves, and the 95% confidence limits were calculated according to the graphic method of Litchfield and Wilcoxon (1949).

Antagonism of morphine analgesia to the tail-flick response was used to evaluate the antagonist potency of our test compounds. In this tail flick assay, the radiant heat method described by D'Amour and Smith (1941) and Harris et al. (1969) had been adapted for use in our laboratory.

RESULTS

Using the computer program LIGAND, a three- and four-site receptor model yielded a self-consistent set of receptor binding affinities and capacities that were statistically much more significant than either a one- or two-site model, but were not significantly different from each other. Results for the three-site model are shown in Table 2 for naloxone, D-ala^2-D-leu^{5}enkephalin (DADL), dihydromorphine (DHM), ethylketocyclazocine (EKC) and the four pairs of resolved 3-phenylpiperidines.

As can be seen by the four standard opioid ligands, sites labeled "μ" and "δ" can be discerned by high affinity of naloxone and DADL respectively. The third site we have chosen to label "κ", however, is not characterized by a high affinity for EKC, which has been called a prototypical κ ligand. Several other investigators however, have noted a lack or limited number of kappa receptors in rat brain (Snyder and Goodman 1980, Gillan and Kosterlitz 1982). This third site contains a much greater number of binding sites than the other two, and may in fact represent a composite of several opioid sites.

The 3-phenylpiperidines are μ-selective, binding with highest affinity at μ and lowest at δ. For the μ site, the affinities range from 18.4 to 424 nM for the (+) enantiomer and from 46.5 to 351 nM for the (-) enantiomer. There is no striking difference in affinity between (+) and (-) enantiomers at any site for any compound.

The similarity in affinities of the enantiomer pairs is in contrast to the striking differences obtained in the mouse acetic acid writhing and antagonism of tail flick analgesia tests (Table 3). The most obvious difference is apparent in the antagonist assay. For all four pairs, the (+) isomers show activity, while the (-) isomers are inactive up to 80 mg/kg (~300 μmol/kg). In contrast to the fused-ring opiates, the (+)-N-phenethyl analog (+)-5 is the most potent antagonist. This compound is 6.5 times less potent than nalorphine and 8-10 times more potent than the other 3-phenylpiperidines tested. For analgesic agonist activity, the N-methyl and N-phenethyl analogs display no stereospecificity, while the (-) isomers of the allyl, 3, and cyclopropylmethyl, 4, are at least 10 times more potent than the (+) isomers. In fact, the (+)-N-cyclopropylmethyl analog, (+)-4, was inactive as an analgesic.

TABLE 2. Receptor affinities and maximum binding capacities for a three-receptor site model

	K_D (nM)		
	"μ"	"δ"	"κ"
DADL	4.74 ± 0.34	1.40 ± 0.32	1060.0 ± 237.0
Naloxone	0.83 ± 0.06	18.30 ± 2.44	26.30 ± 3.43
EKC	1.27 ± 0.09	9.80 ± 1.42	288.0 ± 36.2
DHM	1.32 ± 0.11	91.70 ± 13.20	86.20 ± 12.00
N-methyl			
(-)-3	351.0 ± 25.5	19200.0 ± 1960.0	5580.0 ± 598.0
(+)-2	424.0 ± 32.5	12700.0 ± 1710.0	4610.0 ± 635.0
N-allyl			
(-)-3	64.4 ± 6.4	3327.0 ± 416.0	1305.0 ± 200.0
(+)-3	194.5 ± 127.0	2555.0 ± 355.0	1299.0 ± 340.0
N-cyclopropylmethyl			
(-)-4	46.5 ± 4.68	2140.0 ± 272.0	489.0 ± 93.3
(+)-4	148.2 ± 16.3	1113.0 ± 135.0	621.8 ± 173.0
N-phenethyl			
(-)-5	47.3 ± 7.30	1824.0 ± 724.0	1381.0 ± 308.0
(+)-5	18.6 ± 3.30	420.5 ± 74.0	1373.0 ± 282.0
B_{max} (pmol/g)	17.0 ± 1.0	5.7 ± 0.9	143.0 ± 16.4

DISCUSSION

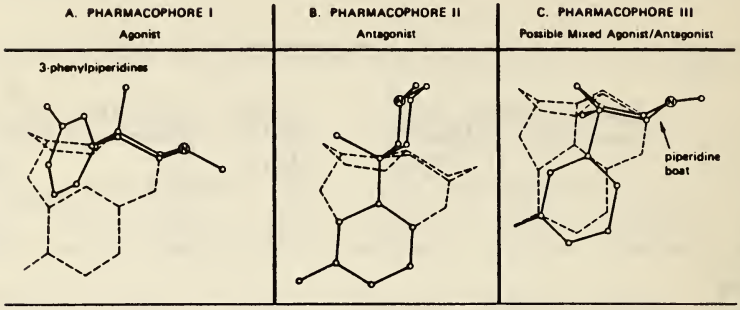
The major finding in our study of binding affinities and analgesic and antagonist activity of resolved 3-(m-OH)phenylpiperidine compounds is that while receptor affinities do not vary significantly between enantiomers at any site, all of the antagonist activity resides in the (+) isomer of each enantiomeric pair. Some stereospecificity is also apparent in the analgesic activity of the N-cyclopropylmethyl and N-allyl analogs, but not in N-methyl or N-phenethyl compounds. These results indicate that determination of receptor affinity, at least at the sites we have characterized, is not sufficient to predict differences in agonist or antagonist activity.

TABLE 3. Analgesic and narcotic antagonist potencies of resolved 3-methyl-3-m-hydroxyphenylpiperidine with N-substituent variation

	Mouse Writhing Test[a] ED_{50} (95% Confidence limits) µmol/kg i.p.	Mouse Tail-Flick Test[b] Antag ED_{50} (95% C. limits) µmol/kg i.p.
N-Methyl		
(-)-2	25.69 (14.68 - 44.96)	c
(+)-2	41.36 (21.55 - 79.42)	101.34 (71.35 - 143.90)
N-Allyl		
(-)-3	14.34 (8.96 - 22.94)	c
(+)-3	160.94 (106.58 - 243.02)	112.02 (69.58 - 180.36)
N-Cyclopropylmethyl		
(-)-4	12.23 (2.83 - 21.41)	c
(+)-5	d	139.32 (83.93 - 231.27)
N-Phenethyl		
(-)-5	18.38 (11.08 - 30.52)	c
(+)-5	11.53 (7.21 - 18.44)	13.07 (8.71 - 19.58)
Morphine Sulfate	0.81 (0.51 - 1.29)	
N-Allylnormorphine Hydrochloride		2.04 (1.44 - 2.87)

[a] Inhibition of acetic acid induced writhing.
[b] Antagonism of tail-flick inhibition induced by morphine sulfate (21.08 µmol/kg, s.c.)
[c] Compounds showed no significant antagonist activity up to dose of 80 mg/kg.
[d] Showed no significant activity at a dose of 707.21 µmol/kg.

FIGURE 1. Postulated 3-phenylpiperidine agonist and antagonist pharmacophores



Based on energy calculations, binding affinities and agonist and antagonist activities of racemic 3- and 4-phenylpiperidine compounds, we have postulated three possible qualitatively different receptor binding orientations that can lead to agonism and antagonism (Fig. 1) (Lawson et al., In press; Burt and Loew 1984). In these binding modes, an overlap with only the cationic amine nitrogen of morphine (Pharmacophore I) will lead to agonism while an overlap of only the m-OH-phenyl with morphine's phenyl-OH will produce antagonism (Pharmacophore II). Thus mixed agonist/antagonist activity could by accounted for by a single compound binding in a bimodal fashion as in Pharmacophores I and II. N-R variations could then modulate the extent of binding of each isomer in each mode, but in a manner different from that in fused ring opioids. By contrast, if the 3-phenylpiperidines bind in a Pharmacophore III mode with a simultaneous overlap with morphine's amine nitrogen and m-OH-phenyl group, we would expect N-R variations to modulate agonism and antagonism in a manner similar to that in fused-ring opiates.

For the 3-methyl-3-phenylpiperidines, Pharmacophore I or II could involve ϕ-axial or ϕ-equatorial conformers with a piperidine chair. Pharmacophore III involves a piperidine boat conformer, which, while of higher energy than a chair, cannot be ruled out for the receptor site interactions.

The results presented here are most consistent with the hypothesis that different receptor binding modes lead to agonism and antagonism. All (-) isomers are pure agonists and thus would seem to bind preferentially in an orientation without a m-OH-phenyl overlap (Pharmacophore I), prohibiting antagonist activity. The (+) isomers appear to bind in a bimodal fashion with agonist activity initiated by binding in Pharmacophore I and

antagonist activity initiated by binding in Pharmacophore II. The N-R substituents modulate the extent of binding in each mode. They, however, do not modulate agonist/antagonist activity as in fused-ring opioids. In fused-ring opiates, N-methyl compounds rarely show antagonist activity. Also, the N-allyl and cyclopropylmethyl substitutions in this series do not increase antagonist activity as they do in the fused-ring opiates. Thus, Pharmacophore III with simultaneous cationic amine and hydroxy-phenyl overlaps is probably not involved in the binding.

The surprising finding of strict stereospecificity for antagonism but not agonism should provide clues to additional spatial requirements for antagonist activity of 3-phenylpiperidines other than m-OH-ϕ overlap with morphine at the μ opioid receptor. In the two different enantiomers in Pharmacophore II orientation, the amine-N of the piperidine is displaced relative to the crucial m-OH phenyl group. Apparently, only one of the amine positions is compatible with local receptor subsite interactions.

Preliminary X-ray structure determination of the (+)-enantiomer of the m-OCH_3 nor analogue, 1, reveals that the series of active antagonists derived from this compound have a S-configuration as shown in Pharmacophore II (figure 1). Moreover, as shown in this Pharmacophore, it was found that the piperidine ring has a chair conformation and the phenyl ring is equatorial. These X-ray results support the conclusion that bimodal piperidine chair Pharmacophores (I and II), rather than a boat conformation (Pharmacophore III), are involved in receptor interactions. The X-ray determination of the absolute configuration of the active enantiomer further defines the relative position of the crucial amine and phenyl groups in the antagonist binding mode.

EXPERIMENTAL SECTION

Resolution of (±)-1. The free base 1 (8.9 g, 43.5 mmol) in absolute EtOH (70mL) was treated with a solution of (-)-tartaric acid (7.5 g, 50 mmol) in 95% EtOH (55 mL) and the resulting mixture was allowed to stand overnight at room temperature. The salt which formed (7 g) was filtered. After two recrystallizations from 95% EtOH, the enantiomerically pure salt was obtained. The free base was liberated by extracting a pH 10 solution of the tartrate salt with Et_2O (3 x 50 mL). After drying over K_2CO_3, the solvent was concentrated under vacuum to 50 mL, and ether saturated with dry HCl was added drop-wise at 0^oC to precipitate the HCl salt of (+)-1: mp 188-190°C; $[\alpha]_D^{25^o}$ (c=0.5, MeOH) + 11.0°. The combined mother liquors containing amine 1 enriched with (-)-1 were worked up to yield the pure base which was treated with (+)-tartaric acid, and the resulting salt was recrystallized 3 times to yield the enantiomerically pure product in 37% yield. The hydrochloride salt (-)-1 had a mp of 188-190°C; $[\alpha]_D^{25^o}$ (c=0.5, MeOH) - 10.8°.

REFERENCES AVAILABLE ON REQUEST

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Evidence for Separation of Anesthetic Activity From Prototypic Phencyclidine Action in Drug Discrimination by Molecular Modification of Dioxadrol, a Phencyclidine-Like Dissociative Anesthetic

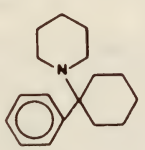
Ernest A. Harrison, Jr.; Michael F. Rafferty; Kenner C. Rice; Cyrus R. Creveling; Gail D. Winger; James H. Woods; and Arthur E. Jacobson

Phencyclidine (1, PCP, figure 1) was synthesized in the late 1950's and found to produce many novel pharmacological and behavioral effects (Chen et al. 1959). Among these was an ability to provide a surgical level of anesthesia with little compromise of respiration or cardiovascular function (Chen and Weston 1960). Unfortunately, PCP produced dysphoric dissociative effects in an unacceptably large percent of the people to whom it was given and its use as an anesthetic was discontinued.

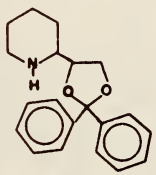
Abuse of PCP has become a serious problem in this country and has caused a resurgence of interest in PCP-like compounds (Henderson 1982, and ref. cited therein). PCP and related compounds have been shown by several laboratories to interact with binding sites or receptors in mammalian brain tissue (Zukin and Zukin 1979; Vincent et al. 1979; Hampton et al. 1982; Rafferty et al. 1984). We, and others, have found that this interaction occurs with reasonably high affinity. Structural specificity and stereospecificity have been demonstrated (Jacobson et al.; Marwaha et al. 1981), and the in vitro affinities of many ligands are in good accord with their in vivo PCP-like actions (Rafferty et al.). We are attempting to characterize the PCP receptor through the synthesis of varied molecules which might have higher affinity or act as antagonists, and we have recently reported the synthesis of an affinity ligand able to bind specifically and irreversibly to the PCP receptor (Rafferty et al. 1984). In our initial efforts to discern molecular requirements for interaction with the PCP receptor, we have hypothesized that the dissociative effects of PCP are mediated through its receptors in the CNS, but that its anesthetic effects may not occur through interaction with that receptor. Thus, compounds which may structurally resemble the PCP-like anesthetics but which do not interact with the PCP receptor may afford us anesthetics without dysphoria.

In 1966, Hardie and colleagues synthesized a large number of 4-(2-piperidyl)-1,3-dioxolanes; compounds which bear little structural resemblance to PCP. One of these, dioxadrol, exists in

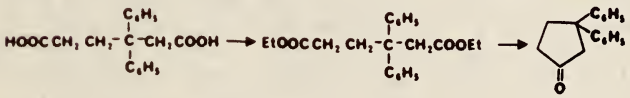
four isomeric forms: alpha (+), alpha (-), beta (+) and beta (-). The alpha (+) and alpha (-), and the beta racemate have potent local anesthetic effects as measured in the rabbit corneal test, and one, dexoxadrol, the alpha (+) enantiomer, had analgesic effects in the rat hot-plate test as well. It was given a clinical trial where it was demonstrated to have analgesic effects but produced dissociative effects very similar to those produced by PCP in a substantial number of patients to whom it was given (Lasagna and Pearson 1965). Dexoxadrol has subsequently been shown to have stimulus properties in common with PCP in squirrel monkeys. It also had limited reinforcing properties in rhesus monkeys, its i.v. presentation producing rates that were above those maintained by vehicle but generally lower than those maintained by PCP (Brady et al. 1982). It has also been shown to bind to the PCP receptor (Hampton et al. 1982) at least as well as PCP (table 1). As shown in figure 1, dioxadrol has two oxygen atoms in its structure.



1 (PHENCYCLIDINE, PCP)



2 (DIOXADROL)
(ALPHA (+)-DIOXADROL=DEXOXADROL)



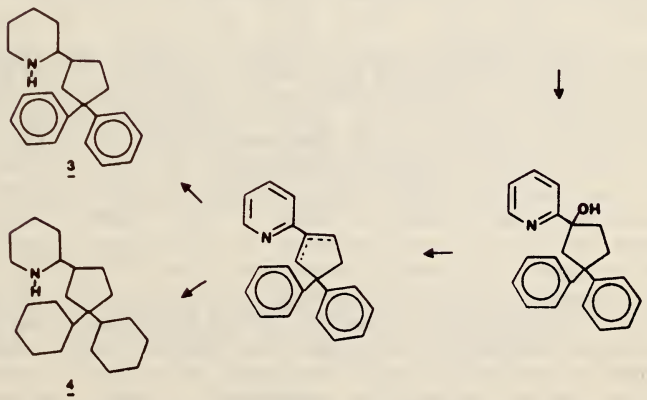


FIGURE 1. Structures of PCP (1) and dexoxadrol (dioxadrol, 2), and synthesis of 1,1-diphenyl-3-(2-piperidyl)cyclopentane (3) and 1,1-dicyclohexyl-3-(2-piperidyl)cyclopentane (4).

We have posed the question of whether these oxygen atoms are necessary for the PCP-like pharmacological actions of dexoxadrol and whether a compound without those oxygen atoms would have anesthetic activity. In order to answer this question, we have synthesized 1,1-diphenyl-3-(2-piperidyl)cyclopentane (3, figure 1), a cyclopentyl analog of dioxadrol, lacking the ether oxygens in dioxadrol's dioxolane ring, measured its interaction with PCP binding sites in vitro, and discerned its similarity to ketamine in a drug discrimination assay. The local anesthetic property of this compound was evaluated as well using batrachotoxin binding as an indicator (Creveling et al. 1983, 1984; McNeal et al. 1984). We have also obtained the dicyclohexyl analog 4 (1,1-dicyclohexyl-3-(2-piperidyl) cyclopentane) as a by-product in the synthesis of 3, and measured its effects in PCP binding and in the local anesthetic assay.

CHEMISTRY

The synthesis of 1,1-diphenyl-3-(2-piperidyl)cyclopentane (3) and 1,1-dicyclohexyl-3-(2-piperidyl)cyclopentane (4) are shown in figure 1; details of the synthesis will be described elsewhere. Their structure was assured by infrared, nuclear magnetic resonance and mass spectroscopy, and by elemental analysis. Compounds 3 and 4 are diastereomeric mixtures; work is in progress on their separation.

BIOLOGY

Batrachotoxin binding - The specific binding of [^{3}H]BTX-B (20 nM, 14 Ci/mmol) to a binding site in voltage dependent sodium channels in a preparation of synaptoneurosomes (Hollingsworth et al. 1984) from guinea pig cerebral cortex was measured in the presence of optimal concentrations of scorpion venom as previously described (Creveling et al. 1983 and 1984; McNeal et al. 1984). Non-specific binding (23%) was determined in the presence of 300 uM veratridine.

Phencyclidine binding assay - Freshly excised rat forebrain (Sprague-Dawley, Taconic Farms) was homogenized for 20 sec in 30 vol ice cold 5 mM Tris.HCl, pH 7.4 (Brinkmann Polytron homogenizer, setting 6). The homogenate was centrifuged at 30,000 x G for 15 min at 4°C, and the pellet resuspended in 30 vol fresh ice cold buffer. The tissue was again centrifuged, and the resuspension and pelleting steps repeated a total of three times. The final washed tissue pellet was then suspended in 80-100 vol of fresh buffer and kept on ice. The assay mixture consisted of 50uL ^{3}H-PCP solution (final concentration 8 nM; specific activity 43.5 Ci/mmole, New England Nuclear), 50 uL buffer, 10 uM PCP (the latter was added to determine nonspecific binding), and 900 uL tissue preparation for a final volume of 1.0 mL. Compounds were added to the buffer in various concentrations for assessment of their displacement of ^{3}H-PCP from the brain. The assay mixtures were incubated at 5°C for 60 min. Separation of bound ligand was accomplished by

filtration of the assay mixture through Whatman GF-B filters which had been soaked for a minimum of two hours in a solution of 0.2% polylysine (MW 150,000-300,000, Sigma) to minimize filter binding of the ^{3}H-PCP. The filters were then washed with 2 x 5 mL aliquots of ice cold buffer. After removing as much liquid as possible from the filters by suction, the filters were transfered to scintillation vials, followed by 8 mL cocktail (Beckman Redisolve). The vials were shaken for 30 min, and allowed to stand for an additional 30 min or longer before counting. The IC_{50} values presented are the average of two separate experiments (each concentration was run in triplicate).

Drug Discrimination - Rhesus monkeys that had been trained to discriminate sc injections of either 1.0 or 1.8 mg/kg of ketamine were used to evaluate the stimulus properties of compound 3. The details of the training and testing procedure have been described elsewhere (Bertalmio et al. 1982; Solomon et al. 1982). During daily sessions, these monkeys were seated in operant conditioning chambers that were equipped with a stimulus light, two response levers and a food receptacle. Ten minutes following the injection of ketamine or a sham injection, the stimulus light was illuminated, and 100 consecutive responses on the appropriate lever were reinforced with delivery of ten 300 mg Noyes banana flavored pellets. The appropriate lever was the right lever if 1.0 or 1.8 mg/kg ketamine had been injected, and the left lever if a sham injection had been given. The stimulus light was turned off after 100 appropriate responses had been made, or after 5 min had passed, which ever came first. If, as was usually the case, responding was completed in less than 5 min, the monkey remained in a blackout period until the 5-min period was completed. A series of 15-min trials, each consisting of a 10-min blackout and a maximum 5-min opportunity to respond, was presented during each daily session. Ketamine was administered on the penultimate trial of a training session, and responding on the right (ketamine appropriate) lever was reinforced on this and the final trial. From zero to four sham trials preceded the ketamine injection, and responding on the left (sham appropriate) lever was reinforced during these trials. During tests of the discriminative effects of compound 3, 100 consecutive responses on either lever was reinforced during each trial of the test session. Increasing doses of compound 3 from 0.03 to 0.32 mg/kg were given in a cumulative fashion, one injection preceding each 10 min blackout period of a trial.

RESULTS AND CONCLUSION

The binding of the various compounds to the PCP receptor can be seen in Table 1, in comparison with PCP and dexoxadrol.

TABLE 1. The affinity of compounds to the phencyclidine receptor in rat brain.

COMPOUND	IC_{50} (nM)
Phencyclidine (1)	95
Dexoxadrol (2)	89
Cyclopentane analog (3)	>1000[a]
Dicyclohexyl analog (4)	>2000

a) 86% inhibition at 10 uM, 47% at 1 uM

Neither the diphenyl-cyclopentane analog of dioxadrol (3) nor the dicyclohexyl-cyclopentane derivative (4) binds to the PCP receptor with any degree of potency. In accord with the binding data, drug discrimination experiments indicate that compound 3 does not act as a PCP-like cue to ketamine-trained animals at doses from 0.03 to 0.32 mg/kg. Monkeys trained to discriminate ketamine from sham injection did not respond on the ketamine-appropriate lever when given increasing doses of compound 3. The rates of responding were not suppressed at the doses tested; the relative insolubility of the compound precluded testing at higher doses. Animals might have generalized to ketamine if higher doses could have been tested. There is, also, a remote possibility that one of the four isomers of 3 is potent in this assay since the diastereomeric mixture in the oxalate salt which was examined biochemically and in vivo appears to be about a 4:1 mixture from thin layer chromatography. Work is in progress on their separation.

Compounds 3 and 4 were tested for their local anesthetic properties by interaction with the voltage-dependent, batrachotoxin binding site in sodium channels. Most local anesthetics have good affinity at that binding site. It was found that compound 3 was about half as potent as dibucaine and that the dicyclohexyl compound 4 was equipotent with dibucaine in that assay; they are among the most potent compounds which have been tested. Although compounds 3 and 4 are diastereomeric mixtures it is, *a priori*, unlikely that one of the isomers will be seen to be very much more potent than the others; little stereospecificity has been noted, heretofore, in this assay.

These preliminary data indicate, however, that one or both of the oxygen atoms in dioxadrol is essential for interaction with the PCP receptor. In conclusion, it appears that while the ethereal oxygens are important for the PCP-like dysphoric activity of dexoxadrol, the in vitro local anesthetic effects persists in the absence of these atoms.

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Dose Effect and Preference Comparison of Diazepam and Oxazepam

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Two experiments were undertaken to provide information about possible differences in the abuse liability of diazepam and oxazepam. The experiments were conducted in a residential hospital research ward setting with male human volunteers with histories of sedative drug abuse. In both experiments, oral doses were administered every third day under double-blind conditions.

In the first experiment, the effects of diazepam (10-160 mg) and oxazepam (30-480 mg) were studied. Dose-effects with area under the time-action curve data (AUC) showed diazepam to be 2.6 to 5.7 times more potent than oxazepam on various psychomotor, cognitive, staff-rated, and subjective measures. Comparison of relative potencies showed diazepam to be relatively more potent in producing liking than in producing psychomotor and cognitive effects. Diazepam produced greater peak effects than oxazepam on a number of staff-and subject-rated measures, including liking. Onset of effect was more rapid and time to maximal effect was shorter (1-2 h vs. 4-12 h) with diazepam than oxazepam, while time to offset of effect was similar for the two drugs. Diazepam was categorized as producing barbiturate-like subjective effects (38.3%) more frequently than was oxazepam (13.8%), while oxazepam was identified as placebo more often than diazepam. Repeated administration of 160 mg diazepam and 480 mg oxazepam showed that AUC liking was greater for diazepam than oxazepam, and that tolerance to psychomotor and cognitive effects occurred with oxazepam but not diazepam. This study suggests that diazepam may have a higher abuse liability than oxazepam.

In the second experiment, the effects of and preference for placebo, oxazepam (480 mg), and diazepam (40, 80, and 160 mg) were studied. After an initial exposure to the letter-coded test drugs, a series of choice days was scheduled on which subjects chose between two available drug alternatives. Compared with oxazepam, diazepam produced greater liking (area under the time-action curve), peak liking and euphoria and was judged to be of greater monetary street value. Diazepam was categorized as producing barbiturate-like subjective effects more frequently than

was oxazepam (54 vs. 21%), whereas oxazepam was identified as placebo more often than diazepam (32 vs. 4%). Diazepam was associated with a more rapid onset of effect than was oxazepam, and this rapid onset was repeatedly cited by subjects in poststudy written comments as being a desirable feature of the drug effect. In choice tests, 80 and 160 mg of diazepam were preferred to 480 mg of oxazepam on 62.5 and 91.7% of the choice tests, respectively. In choice tests between placebo and drug, placebo was never preferred to diazepam; however, placebo was preferred to oxazepam on 21.4% of choice tests. Overall, these results extend the results of the first study suggesting that diazepam has a higher abuse liability than oxazepam.

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Effects of *b*-FNA in Drug-Naive and Morphine-Dependent Rhesus Monkeys

Debra Gmerek and James H. Woods

The β-fumarate methyl ester of naltrexone, β-FNA (Portoghese et al. 1980) has been reported to be a selective non-equilibrium opiate mu receptor antagonist and reversible kappa receptor agonist in vitro (Takemori et al. 1981; Ward et al. 1982a) and in vivo (Messing et al. 1982; Ward et al. 1982b). These properties would make β-FNA very useful as a pharmacologic probe. However, the pharmacology of this interesting compound has not yet been characterized extensively. In this work, we have studied β-FNA by observing its overt behavioral effects in drug-naive and morphine-dependent rhesus monkeys. It was compared to the chemically related narcotic antagonist naltrexone. β-FNA appears to reach sites in the central nervous system after systemic administration in small amounts compared to naltrexone; we find β-FNA to be an insurmountable mu receptor-selective antagonist in the rhesus monkey.

MATERIALS AND METHODS

Subjects

Mature rhesus monkeys (Macaca mulatta) (3.0-5.5 kg) trained to receive s.c. injections were housed in groups of 3-6. Monkeys made dependent by administering morphine (3 mg/kg, s.c.) every 6 hours for a minimum of 3 months were stereotaxically implanted with a stainless steel cannula (Plastic Products) for intracerebroventricular (i.c.v.) injections as described previously (Gmerek et al. 1983). Cannula placements were verified by radiography.

The overt behavior of the monkeys was monitored by two experienced observers familiar with the individual animals. The appearance and actions of the monkeys were recorded every 30 min by checking the presence or absence of particular behaviors and signs on a score sheet. Muscle relaxation is evaluated in terms of the position the monkeys take while sitting still (TABLE 1). Stupor refers to the response of the animals to environmental stimuli. Withdrawal severity grades were made as described previously (Villarreal 1973; Woods et al. 1979) such that higher numerical

scores correspond with an increasing number and severity of withdrawal signs. The morphine-dependent and normal monkeys were tested weekly.

TABLE 1. Scale by which monkeys were graded for general muscle relaxation.

Grade	Appearance
0	No observable muscle relaxation
1	Slight facial relaxation, jaw slackening, shoulder droop
2	Pronounced facial relaxation, jaw slackening, shoulder droop
3	Monkey must brace himself to sit up
4	Monkey cannot sit

Compounds and Injections

β-FNA (Dr. D. Zimmerman, Eli Lilly Co.), morphine sulfate (Merck) and naltrexone HCl (Endo) were dissolved in warm distilled water. Ethylketazocine methanesulfonate (Sterling-Winthrop) was dissolved in a minimal volume of lactic acid and diluted with distilled water. Doses refer to the particular salt. Subcutaneous injections were given in volumes of 0.1-1.5 mls. The monkeys were injected every 30 min with increasing doses of the test agents such that the total cumulative dose increased by ¼- or ½-log units. Intracerebroventricular injections of aseptic solutions were given in volumes of 100 ul, during which time the monkeys were placed in a restraining chair.

RESULTS

Normal Monkeys

Cumulatively administered β-FNA (1.0-10 mg/kg, s.c.) produced stupor and muscle relaxation grades of A and 1, respectively, at 10 mg/kg. The animals (n=6) were at their pre-injection level of appearance and behavior twenty-four hours after 10 mg/kg β-FNA administration.

The effect of naltrexone pretreatment on morphine-induced muscle relaxation is shown in figure 1. Naltrexone (1 mg/kg) caused the expected shift to the right in the morphine dose-effect curves when given 1 hr before morphine, but, when given as a 24-hr pretreatment, even 10 mg/kg of naltrexone was ineffective in antagonizing morphine. Similarly, naltrexone attenuates morphine-induced stupor when given as a 1-hr, but not as a 24-hr pretreatment (Gmerek and Woods 1984). In contrast, 24- and even 48-hr pretreatment with β-FNA (10 mg/kg) antagonized morphine-induced muscle relaxation (figure 2). Morphine-induced stupor is also attenuated by 48-hr pretreatment with β-FNA (Gmerek and Woods 1984). Twenty-four hr pretreatment with β-FNA did not antagonize ethylketazocine-induced muscle relaxation (fig. 3), however. Thus, β-FNA was selective in its ability to antagonize the overt behavioral effects of morphine but not EKC.

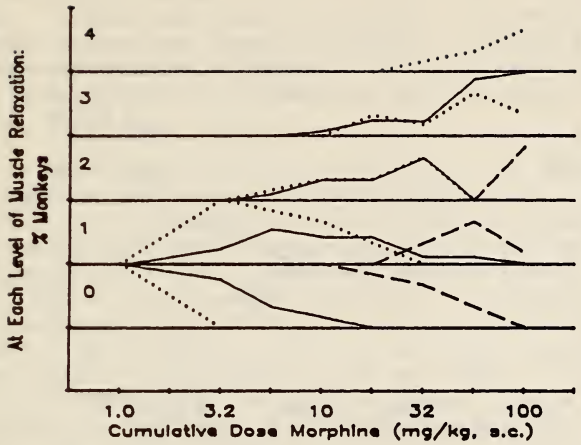

FIGURE 1. The effect of cumulative morphine alone (solid lines), 1 hr after 1 mg/kg naltrexone (dashed lines), and 24 hr after 10 mg/kg naltrexone (dotted lines) on muscle relaxation in normal monkeys (n=6). Each horizontal segment represents the percent of monkeys (from 0-100%) showing the level of muscle relaxation indicated as described in table 1.

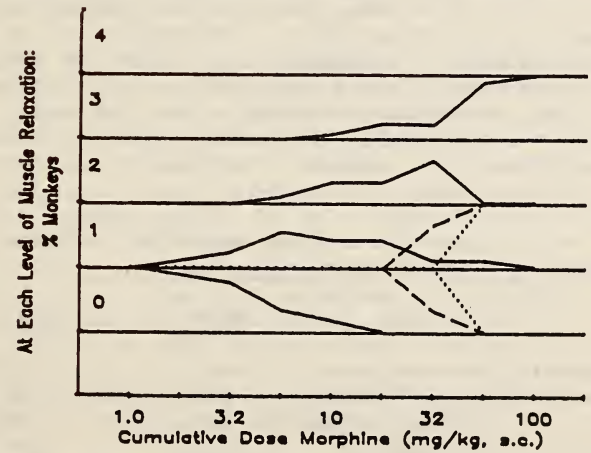

FIGURE 2. The effect of cumulative morphine alone (solid lines) and after 24-hr (dashed lines) or 48-hr (dotted lines) pretreatment with 10 mg/kg β-FNA on muscle relaxation in normal monkeys (n=6).

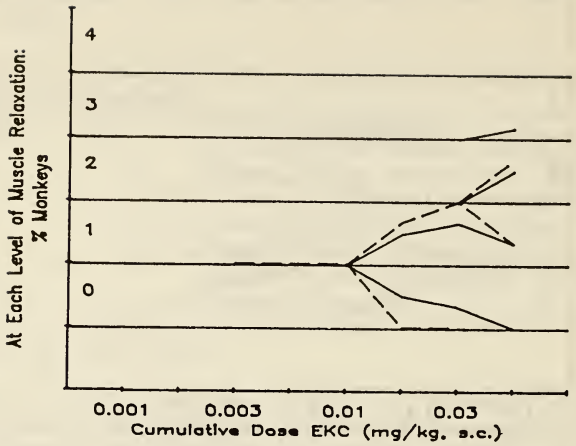

FIGURE 3. The effect of cumulative ethylketazocine (EKC) alone (solid lines) and 24 hr after 10 mg/kg β-FNA on muscle relaxation in normal monkeys (n=6).

Morphine-Dependent Monkeys

Single doses of β-FNA (1, 3.2 and 10 mg/kg, s.c.) precipitated withdrawal in a dose-related fashion in morphine-dependent monkeys. Table 2 compares the dose of naltrexone and β-FNA required to precipitate withdrawal of equivalent severity after s.c. and i.c.v. administration. Subcutaneously administered β-FNA was significantly less potent than s.c. naltrexone in its ability to precipitate withdrawal, whereas i.c.v. β-FNA was more potent than i.c.v. naltrexone. Taking into consideration the weight of the monkeys (i.e., converting mg/monkey, i.c.v. to mg/kg, i.c.v.) β-FNA was approximately 16,000 times more potent by i.c.v. than s.c. administration. In contrast, naltrexone was essentially equipotent by the two routes.

TABLE 2. Duration of withdrawal of equivalent severity in morphine-dependent monkeys (r=6).

Method	Dose	Route	Duration *
14-h deprivation	----	----	24 hr
naltrexone	0.01 mg/kg	s.c.	36 hr
β-FNA	10.0 mg/kg	s.c.	96 hr
naltrexone	0.056 mg	i.c.v.	<24 hr
β-FNA	0.003 mg	i.c.v.	120 hr

*In the presence of normal maintenance doses of morphine (3 mg/kg, s.c. every 6 hr).

The time-course of precipitated and natural withdrawal was determined by monitoring the monkeys until they ceased to show signs of abstinence. During this time the monkeys continued to receive their normal maintenance doses of morphine (3 mg/kg, s.c. every 6 hr). β-FNA-precipitated withdrawal lasted substantially longer than that precipitated by naltrexone or produced by 14 hr morphine deprivation (TABLE 2).

In order to assess the relative reversibility of β-FNA and naltrexone, morphine was given (cumulative doses of 1, 3, 10, 17.5, 32, 56, 100, 185, 320 mg/kg, s.c.) at 30-min intervals beginning 1 hr after the precipitation of equivalent levels of withdrawal by s.c. naltrexone or β-FNA. Dependent monkeys undergoing 14-hr natural withdrawal were treated similarly. A cumulative dose of 17.5 mg/kg morphine completely suppressed the withdrawal elicited by naltrexone (0.01 mg/kg, s.c.) or by 14-hr abstinence. An equivalent level of withdrawal induced by β-FNA (10 mg/kg, s.c.) was slightly attenuated by 320 mg/kg morphine. These monkeys had dilated pupils, slight stupor and mild muscle relaxation, but continued to show other signs of withdrawal. Morphine also did not suppress i.c.v. β-FNA (0.003 mg) precipitated withdrawal (Gmerek and Woods 1984). Thus, β-FNA-induced withdrawal was essentially insurmountable.

DISCUSSION

Using observational methods in drug-naive rhesus monkeys, we have shown that β-FNA is a long-lasting antagonist of morphine but not the kappa agonist EKC. In dependent monkeys, β-FNA precipitates long-lasting withdrawal which is insurmountable by subsequent morphine administration. We also find that there is a large s.c./i.c.v. potency difference for β-FNA.

Naltrexone is effective as an antagonist of the acute behavioral effects of the mu agonist morphine (vida supra) and as well as the kappa agonist EKC (Gmerek and Woods 1984) in normal monkeys. β-FNA, however, at the time it was an effective antagonist of morphine-induced muscle relaxation, did not antagonize EKC-induced muscle relaxation. This suggests that, in agreement with Ward et al. (1982b), β-FNA appears to be a selective mu antagonist *in vivo*. β-FNA also has a long duration of action. The withdrawal elicited by β-FNA in morphine-dependent monkeys lasted about twice as long as a similar level of withdrawal precipitated by naltrexone. The duration of β-FNA-induced withdrawal is in agreement with the results of Aceto et al. (1984) and may correspond with the length of time required to regenerate new opiate receptors. However, a long duration of actions is only indirect evidence of irreversibility, and may be misleading (see Woods et al. 1984).

The ability of morphine to overcome β-FNA precipitated withdrawal was therefore examined. In contrast to natural abstinence and that precipitated by the competitive antagonist naltrexone, as well as naloxone, Win 44,441, MR 2266 and cyclazocine (Gmerek 1984), β-FNA-precipitated withdrawal could not be completely

suppressed by subsequent morphine administration. This provides evidence of the insurmountability of β-FNA in vivo.

There are a number of possible explanations for the large potency difference of β-FNA according to route of administration (i.e., s.c. or i.c.v.). The first is that β-FNA may be metabolized after systemic injection. The possibility that β-FNA is inactivated cannot be discounted. A second possibility is that β-FNA has difficulty penetrating the blood-brain barrier. However, β-FNA is thought to pass the blood-brain barrier readily (Dr. P. Portogehese, personal communication). A third possible explanation for the low potency of β-FNA after s.c. injection is that there may be a significant amount of non-brain site binding, such as to plasma proteins. This would thereby lower the concentration of β-FNA available to enter the central nervous system after systemic administration.

In summary, large doses of β-FNA are required in order to be effective after s.c. administration. However, β-FNA does appear to be a mu-selective insurmountable antagonist in the rhesus monkey.

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Experimental Assessment of the Relative Abuse Liability of Triazolam and Pentobarbital

John D. Roache and Roland R. Griffiths

There has been increasing interest in assessing the abuse liability of benzodiazepines relative to the barbiturates and determining whether there are differences between individual benzodiazepines in terms of abuse liability (Griffiths & Roache, 1984). One of the best validated human experimental methodologies for providing information relevant to abuse liability is to evaluate the subjective and/or reinforcing effects of psychoactive substances in subjects with histories of drug abuse. Commonly, the abuse liability of a test drug is inferred by the degree of subjective "euphoric" effects the test drug may produce in comparison to a standard drug of known abuse liability such as pentobarbital (Jasinski et al., 1982, 1983). Subjective "euphoric" effects are often assessed through the use of standardized factor scale questionnaires such as the Addiction Research Center Inventory (ARCI) or through single item ratings such as a question of drug liking (Griffiths et al., 1983, 1984).

The present report describes findings from a recent study which compared the effects of triazolam (TZ) (a benzodiazepine hypnotic) and pentobarbital (PTB) in subjects with histories of sedative drug abuse. The experimental approach involved both the assessment of the liability for abuse (likelihood) through the use of subject rating scales and the assessment of the liability of abuse (associated hazard) through the use of objective performance measures and subject ratings of task performance.

METHODS

Using a double-blind, 9 X 9 latin square design, the effects of placebo, TZ (0.5, 1.0, 2.0, 3.0 mg), and PTB (100, 200, 400, and 600 mg) were examined in nine male volunteers (20-40 yrs; 70-100 kg) living on a residential research ward. All subjects had documented histories of drug abuse and were not physically dependent at the time of the study. The daily experimental protocol ran from 0800-2200 hrs during which time subjects participated in procedures, completed questionnaires, and performed tasks similar to those in former studies from this laboratory which have been previously described in detail (Griffiths et al., 1983, 1984). Each day, subjects were not

permitted to eat solid foods until 1300 hrs and the placebo vehicle was administered as an unsweetened powdered fruit drink mixture at 1000 hrs. After a 4-7 day acclimation period, test doses of placebo or drug were administered in the vehicle on every second day. Data were analyzed by ANOVA coupled with Duncan's New Multiple Range Tests for post-hoc comparisons. Relative potencies were calculated by the method of Finney (1964).

RESULTS

Both TZ and PTB produced comparable degrees of dose-related impairment as measured by staff (observer) ratings of drug effect and drug-induced drunkenness and also by two objective measures of psychomotor performance, circular lights and a computerized version of the digit-symbol-substitution task (DSST) (a psychomotor task involving a cognitive component). A similarly rapid onset of action was observed with both TZ and PTB although the peak effect of PTB (2-3 hrs) lagged somewhat behind that of TZ (1-2 hrs). TZ tended to produce greater peak effects than PTB but had a shorter duration of action (< 8 hrs) than PTB (> 12 hrs). Analysis of peak effect and area under the time-action curve (AUC) data from these staff ratings and objective performance measures indicated that the dose-effect curves for the two drugs were parallel and roughly comparable; relative potency calculations indicated that TZ was approximately 200 times more potent than PTB (the range across these measures was 159.24-273.94).

In contrast to the similarity in the effects of TZ and PTB observed with staff ratings and the above-mentioned performance tasks, subject ratings of drug effect and drug-induced drunkenness indicated that TZ produced effects of a reduced magnitude and a distinctly shorter duration (4-6 hrs for TZ and 12 hrs for PTB). The reduced subject ratings of TZ's duration resulted in significant drug differences with the AUC data; the peak effect differences were not significant although relative potency calculations indicated a reduced potency differential (134.77-153.61) between TZ and PTB. A possibly related observation was obtained with the subject estimates of performance on the circular lights and DSST tasks. Subjects were "blinded" as to their actual scores on these tasks but were asked to estimate how well they did by placing a mark on a 100 mm visual analog scale labeled from "much worse" to "much better" than normal. With this measure, subjects consistently underestimated the degree of impairment produced by TZ, whereas they more accurately estimated the degree of PTB-induced impairment.

Two additional performance tasks utilized in the present study were an immediate and a delayed recognition memory task. With both tasks, memorization occurred at 1.5 hrs post-drug; with the delayed recognition task, subjects were tested the following morning after drug effects had dissipated, whereas, with the immediate recognition task, subjects were tested within minutes of acquisition. With both tasks, TZ produced significantly greater amnestic effects than PTB; with the delayed test, even the 0.5 mg dose of TZ produced nearly maximal effects.

In order to assess the liability (likelihood) for abuse of TZ, several subject rating scales were utilized in the present study. One rating scale involved the use of a five-point scale on which subjects could repeatedly rate the degree to which they liked the way the drug made them feel throughout the 24-hr post-drug period. Analysis of the AUC data for this measure indicated that TZ was less well liked than PTB. Examination of the peak effects showed that there was a nonsignificant tendency for PTB to result in a greater peak degree of drug-liking than TZ and the relative potency calculation showed that TZ was 122.16 times more potent than PTB on this measure. Three other rating scales were completed by subjects at 0830 hr of the morning following the day on which drug was administered. At this time, subjects were asked to rate (on a 100 mm visual analog scale) the degree to which they "liked" or "would choose to take again" the "drug you took yesterday", and were asked to estimate the monetary street value of yesterday's drug. With all three of these scales, PTB was generally rated higher than TZ although the drug differences were not statistically significant. The 400 and 600 mg doses of pentobarbital were consistently rated higher than the 3.0 dose triazolam on the visual analog ratings of liking and choose to take again. With the estimated street value, 600 mg of pentobarbital was rated as worth \$8.06 ($\pm$ 2.90, S.E.M.) whereas 2.0 and 3.0 mg of triazolam were rated as worth only \$4.88 ($\pm$ 1.78, S.E.M.) and \$3.42 ($\pm$ 1.01, S.E.M.) respectively; the difference between 600 mg pentobarbital and 3.0 mg triazolam was significant. Relative potency calculations showed that with these three rating scales, TZ was found to be 91.23-122.26 times more potent than PTB.

DISCUSSION

The present study provides important information relevant to the assessment of the abuse liability of TZ by providing within-subject comparisons to PTB in a procedure which enabled the simultaneous examination of measures of subjective effects and objective behavioral performance. The results clearly indicate that with acute dosing, TZ has a lower liability (likelihood) for abuse than PTB. This conclusion is based upon the finding that subjects with histories of drug abuse rated TZ as being less well liked, having a lower street value, or as being a drug they would be less likely to choose to take again. The relative potency calculations showed that in comparison to PTB, TZ was relatively less potent in producing these effects (relative potency range: 91.23-122.26) than in producing performance impairment (relative potency range: 159.24-273.94). While the likelihood of abuse of a drug is dependent on other factors besides reinforcing properties (i.e., availability), the value of a subject rating scale is in the extent to which it predicts "pleasant" subjective effects which may be related to reinforcing properties. The subject rating scales utilized in this study are presumed to reflect reinforcing properties of drugs in that if the drug effect is "liked" or thought to have "street value" then one would predict that the drug may be self-administered.

Also important to abuse liability assessment is a determination of the liability of abuse, in other words, the deleterious (hazardous or

toxic effects) consequences of abusive drug usage (Brady & Griffiths, 1982). Clearly, the greatly reduced likelihood of respiratory depression with TZ has to be considered an advantage of TZ. However, the results of the present study indicate that with regard to performance impairment, TZ may have a liability greater than that of PTB. The finding that in comparison to PTB, subjects under the influence of TZ rated themselves as less affected and less impaired even though they were similarly impaired (by objective criteria) suggests that under-estimation of impairment may be greater with TZ.

The role of drug-induced amnesia in abuse liability is unclear. Certainly, the dramatic amnestic effect observed with even the lowest dose of TZ indicates a greater liability associated with its use. It is also possible that such an effect may influence the reinforcing properties of TZ; for example, several subjects spontaneously indicated that they would not use this drug on the street because they could not remember what happened and would not like to wake up in jail not knowing what they had done. Therefore, it is possible that amnestic effects of TZ may reduce the liability for abuse for some individuals.

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Behavioral Dependence in Rhesus Monkeys Following Chronic THC Administration

P. M. Beardsley; R. L. Balster; and L. S. Harris

The principal behaviorally active component within cannabis products is delta-9-tetrahydrocannabinol (THC). Over the last two decades there have been conflicting reports whether or not a withdrawal syndrome is associated with abstinence from THC. Many studies have been unable to observe behaviors characteristic of withdrawal from THC (e.g., Chesher and Jackson 1974; Dewey et al. 1972; Harris et al. 1974; Leite and Carlini 1974; McMillan et al. 1970) while others have been able to do so (e.g., Deneau and Kaymakcalan 1971; Fredericks and Benowitz 1980; Jones and Benowitz 1976; Stadnicki et al. 1974). There are a number of differences between those studies which have and have not been able to observe abstinent behaviors including differences in dosing regimen, species of subjects tested, and route of administration. Perhaps the crucial variable responsible for the inconsistent observation of withdrawal-associated changes, however, is that different behaviors are monitored from study to study for detection of withdrawal effects. For example, when behaviors characteristic of the stereotypical withdrawal syndromes associated with the narcotics or the sedative-hypnotics are monitored, abstinent syndromes are not observed (Dewey et al. 1972). In some studies, however, that have examined performance of learned behaviors as the method for detecting abstinent-specific changes, withdrawal effects have been observed (e.g., Branch et al. 1980). In general, the sensitivity of the baseline used to monitor THC withdrawal changes may be the determining factor whether or not they are observed. Baselines composed of schedule-controlled behavior can be used as sensitive instruments to assess both the effects of drug administration and the effects of discontinuing a drug's administration. For example, marked alterations in schedule-controlled behavior, indicative of withdrawal, have been demonstrated following the discontinued administration of morphine in rhesus monkeys and rats (Ford and Balster 1976; Holtzman and Villarreal 1973; Thompson and Schuster 1964),

of phencyclidine in rhesus monkeys (Slifer et al. 1984), and following abstinence from prolonged ethanol drinking in rats (Ahlenius and Engel 1974). In this study we report the effects during abstinence from continuous infusion regimens of THC on schedule-controlled behavior of rhesus monkeys.

METHODS

Four adult, male rhesus monkeys (Macaca mulatta) served as subjects. Each monkey had been used in a previous study involving the effects of intravenous phencyclidine administration and withdrawal (Slifer et al. 1984). All of the monkeys had been drug free for at least 3 months prior to the start of the present experiment. The animals were individually housed in enclosed, fiber glass cubicles (0.8m x 0.8m x 1.0 m) equipped with filtered ventilation systems. Each monkey wore a stainless steel tubular harness with a connected spring arm. The spring arm was attached to the rear of the cubicle. The harness and spring arm prevented the monkey from leaving the cubicle but allowed free movement within the cubicle. The monkeys were surgically prepared with chronically indwelling catheters under phencyclidine-pentobarbital anesthesia. The silicone rubber catheter (0.8 mm lumen) was inserted into either a femoral, internal jugular, or external jugular vein. The distal end of the catheter was passed subcutaneously to an exit point on the animal's back. The external catheter was then threaded through the spring arm and out the rear of the cubicle where it was connected to a syringe infusion pump.

Within the cubicle, two response levers were located on the clear Plexiglas door at the front of the chamber. Two red and one white 28v lamps were mounted above each lever. A food hopper was located between the response levers. Events within the chamber were controlled and recorded by solid-state programming equipment located in adjacent rooms.

The monkeys had extensive experience pressing the right lever for banana pellets under either a FR 100 (Monkeys M321 and 6189) or a FR 150 (Monkeys M320 and 7623) schedule of reinforcment. Responses on the left lever did not have scheduled consequences. The monkeys could obtain banana pellets according to their respective reinforcement schedules during four daily, 30-min sessions that began at 4:00 p.m., 10:00 p.m., 4:00 a.m., and 10:00 a.m. During each session the lights above the right lever were illuminated. In addition, a white-noise alarm was sounded at the start of each session and was terminated by the first press of the right lever.

Following surgery, saline was continuously infused via the catheters at a rate of 1.0 ml/hr. After a minimum of three days, saline was replaced with a solution of Emulphor 620, 95% ethanol, and 0.9% saline in a ratio of 1:1:8, respectively. This concentration was chosen since it is able to serve as a vehicle for up to 20 mg/ml of THC (Carney et al. 1977).

Vehicle solutions were replaced by 0.05 mg/kg/hr THC following five days of stable food-reinforced responding. After 10 days of 0.05 mg/kg/hr THC infusion, vehicle was again administered until behavior recovered. This procedure involving predrug vehicle for at least 5 days, 0.05 mg/kg/hr THC for 10 days, followed by postdrug vehicle was repeated for Monkeys 7623, M321, and 6189 (referred to as the Second Determination). Monkey M320 was additionally tested under a 16-day drug regimen of 0.05, 0.075, 0.113 and 0.169 mg/kg/hr THC for 2, 2, 2, and 10 days, respectively.

Routine housekeeping (cubicle cleaning, watering, and animal inspections) was performed between 7:00 and 8:30 a.m. daily. Solution changes occurred at 2:00 p.m., two hours prior to the first session of the day. It was estimated that this syringe change time would enable the new solution front to arrive at the catheterized vein concurrently with the start of the 4:00 p.m. session. Stock solutions of THC (100 mg/ml) were prepared using a solvent composed of Emulphor 620 and 95% ethanol in a 1:1 concentration. Working drug solutions were prepared using appropriate amounts of stock solution dissolved in 0.9% saline.

RESULTS

Response rates during the final day of THC administration were higher than on the final day of predrug vehicle administration for Monkeys 7623 and M321 during Determinations 1 and 2, and for M320 during Determination 1 and during his 16-day regimen (see table 1). Monkey 6189 responded at a lower rate on the last day of THC administration than on the last day of predrug vehicle during Determination 1; however, this was atypical of his overall performance. Usually the response rate of Monkey 6189 on drug days was within the range of his predrug response rates during both determinations. While the monkeys were receiving THC administration it was often difficult to detect observable drug effects in the gross behavior of the animals. The finding that response rates were either equal to and often higher than predrug vehicle rates, in addition to the observation that few changes in gross behavior were observed during THC administration periods, provides evidence that these regimens of THC administration were not particularly debilitating.

Table 1 shows that within 48 hours following withdrawal of 0.05 mg/kg/hr THC there occurred sharp reductions in response rates to below predrug and drug levels for Monkeys 7623, M321, and 6189 during both the First and Second Determinations. Monkey M320 did not show reductions in response rates comparable to the other monkeys following the 10-day 0.05 mg/kg/hr regimen; however, response rate reductions to near-zero levels occurred within 72 hours following the 16-day drug regimen in this monkey.

TABLE 1

The Effects of Delta-9-THC Administration and Withdrawal on Food- aintained Responding (mean daily lever presses/sec)

Monkey	Final Day PreDrug Vehicle	Final Day THC	Withdrawal Day 1	2	3	10
			Determination 1			
7623	2.9	3.1	3.2	0.8	0.2	1.8
M321	1.7	2.5	2.1	0.2	0.2	0.0
6189	2.2	1.0	0.4	0.7	0.5	1.5
M320	2.2	2.5	2.8	2.8	2.7	2.9
			Determination 2			
7623	2.3	2.8	2.6	0.5	0.8	2.5
M321	2.1	2.7	2.9	0.2	0.3	1.4
6189	2.1	2.1	0.8	0.6	0.9	1.5
			16-Day Regimen			
M320	2.9	3.0	2.8	0.3	0.0	1.7

Figure 1 shows daily mean lever presses per second for Monkey 7623 during the First and Second Determinations. Response rates within Determination 1 during the predrug and drug periods were similar and usually exceeded 2.75 lever presses/sec. On the first day of withdrawal during Determination 1, the mean response rate was still within the range of response rates observed during the drug period. During the second day of withdrawal, however, response rates dropped sharply and decreased again on the third day of withdrawal to below 0.25 lever presses/sec. Thereafter response rates increased through the 16th day of withdrawal, whereupon lever pressing rates began to restabilize at around 2.5 responses/sec. Similar effects were seen during Determination 2 except response rates slightly increased from the predrug to the drug period and maximum reductions in response rates were seen by the second day of withdrawal.

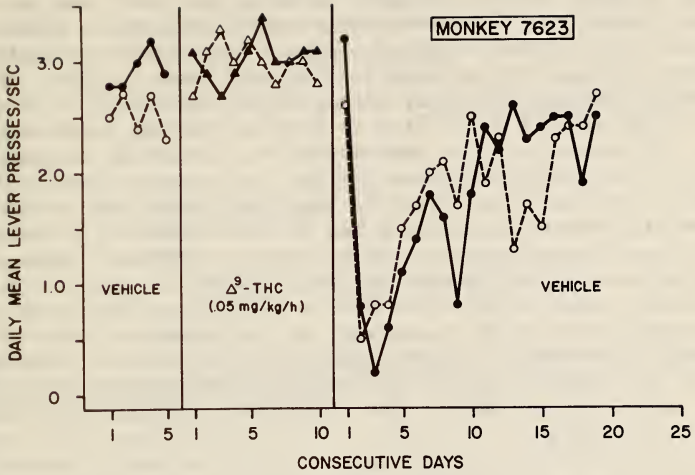

FIGURE 1. Effects of continuous i.v. infusion and withdrawal of delta-9-THC on responding maintained by food presentation for Monkey 7623. Each point is the mean of four daily 0.5-hr food sessions. Filled symbols: First Determination. Unfilled symbols: Second Determination.

DISCUSSION

Three of the four monkeys showed marked withdrawal disruption of their food-maintained responding following a 10-day regimen of 0.05 mg/kg/hr of THC. Monkey M320, who did not show response rate changes upon withdrawal following the 10-day regimen, did so when the dose and duration of contact with THC was increased. It is important to note that these drug regimens did not involve debilitating administrations of the drug as evidenced by the fact that response rates usually were maintained or increased during the drug period relative to the predrug period. In fact, a regimen involving 0.05 mg/kg/hr (i.e., 1.2 mg/kg/day) is within the range of drug administration observed in some chronic users of cannabis products (LeDain et al. 1972)). It is surprising that histories involving such low doses of THC are sufficient for generating withdrawal-reduction of food-maintained responding in the magnitude observed in the present experiment, although other studies involving the use of laboratory animals and human subjects have observed reductions in food intake following discontinuation of the administration of THC and cannabis products (Deneau and Kaymakcalan 1971; Jones and Benowitz 1976; Greenberg et al. 1976).

The underlying behavioral mechanisms responsible for the THC withdrawal-reduction in food-maintained responding are unclear. At least two mechanisms are possible. One possibility is that the monkeys were incapacitated during withdrawal such that most operant behavior (including lever pressing for food) was suppressed. If this had occurred other marked changes in behavior would likely have been evident. However, behaviors indicative of motor incapacitation were usually not seen. Also, when responding for food did occur during withdrawal, local response rates during each FR were often as high as predrug local response rates. If the monkeys had been suffering from motor incapacitation, local response rates should have been dramatically reduced. A second possibility is that the disruption is specific for food-maintained responding due to some type of anorexia. Often in routine observations done during withdrawal, however, the monkeys would eat banana pellets offered to them by hand. Nevertheless, this observation does not eliminate the possibility that anorexia did contribute to the behavioral mechanism responsible for response-rate reductions. Additional research needs to be conducted to clarify what behavioral mechanisms of action were responsible for the response-rate reductions seen during withdrawal.

The suppression of responding following the discontinued administration of delta-9-THC was an effect seen in all four monkeys. Disruption of operant responding following termination of chronic drug administration is evidence for behavioral dependence (Schuster and Thompson 1969). This study has demonstrated that monkeys can become behaviorally dependent upon delta-9-THC and has provided another example of the utility of using operant baselines to assess the effects of withdrawal from drugs.

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Alcohol Self-Administration as a Function of Menstrual Cycle Phase

N. K. Mello; M. P. Bree; and J. H. Mendelson

INTRODUCTION

Recently we reported that female rhesus monkeys are an excellent model for studying the effects of alcohol on reproductive function (Mello et al. 1983). During chronic alcohol self-administration, female rhesus monkeys develop derangements of reproductive function similar to those seen in alcoholic women (Mello et al. 1983). Alcohol dependence in women and female rhesus monkeys has been shown to be associated with amenorrhea, anovulatory cycles, and luteal phase inadequacy (Hugues et al. 1980; Moskovic, 1975; Ryback, 1977; Mello et al. 1983). In the context of these endocrine studies, we also examined the co-variance between alcohol self-administration and menstrual cycle phase in female rhesus monkeys.

Clinical studies of women with alcohol problems have consistently shown that drinking tends to increase during the premenstrual phase of the menstrual cycle (Podolsky, 1963; Belfer and Shader, 1976; Belfer et al. 1971). Patients who reported premenstrual tension used alcohol to attempt to decrease or modulate the unpleasant symptoms associated with the premenstruum. To date, there have been no empirical studies of the temporal concordance between drinking, mood, and hormonal changes associated with the menstrual cycle in female alcoholics or in problem drinkers (cf. Mello, 1980 for review).

Although there is abundant clinical evidence that dysphoric mood states in women are correlated with certain menstrual cycle phases (Moos, 1969; Smith, 1975; Steiner and Carroll, 1977), the reality of the premenstrual tension syndrome has often been challenged on methodological as well as idealogical grounds (Wilcoxon et al. 1976; Rubinow and Roy-Byrne, 1984). For example, it is sometimes argued that women experience discomfort because they have been taught that they should feel premenstrual tension and anxiety (Ruble, 1977). At the other end of the spectrum are those who postulate that the cyclic changes in pituitary gonadotropins and

ovarian steroid hormones which define the phases of the menstrual cycle may contribute to changes in affective states (Bardwick, 1975; Dalton, 1964; Steiner and Carroll, 1977; Reid and Yen, 1981). How subjective changes in feeling states are influenced by expectancy or modulated by concurrent changes in pituitary and gonadal hormone secretory patterns is unknown. It is not known if any phase of the menstrual cycle is associated with discomfort in female monkeys. However, any consistent covariance between alcohol self-administration and menstrual cycle phase in monkeys could not reasonably be attributed to learning or expectancy factors.

METHODS

Sexually mature female Macaque monkeys (4.6 to 7.5 kg) were housed individually in a room with adult males. A 12-hour light-dark cycle (7 a.m. to 7 p.m.) was in effect. During adaptation to the laboratory, monkeys were maintained on ad lib food and water. Daily supplements of fresh fruit, vegetables and multiple vitamins were given throughout the study. Vaginal swabs were done daily to determine the onset and duration of menstrual bleeding. Blood samples were collected two or three times each week for radioimmunoassay of pituitary and gonadal hormones and to determine levels of alcohol in blood. Details of radioimmunoassay and blood alcohol analysis methods have been published (Mello et al. 1984a). Monkeys were periodically evaluated with laboratory tests to monitor the status of liver function, lipid and carbohydrate metabolism, electrolyte homeostasis and hematologic function.

Each monkey had a prior history of occasional alcohol exposure in studies of the acute effects of alcohol on pituitary gonadal hormones (Mello et al. 1984a) but had been alcohol free for at least three months prior to initiation of the behavioral studies. All monkeys appeared to have normal ovulatory menstrual cycles as indicated by a mid-cycle luteinizing hormone (LH) surge and subsequent elevation in progesterone levels.

Monkeys were trained to work for food in an operant paradigm on gradually increasing response requirements on a variable ratio (VR) schedule in which the number of responses required for each reinforcement varied irregularly. An average of 16 responses (VR 16) produced a brief stimulus light (S+) and a 1 gram banana pellet. When response behavior was stable, a second order schedule was used where only a brief stimulus light (S+) was delivered after completion of each VR 16 response requirement. After four consecutive VR 16 components were completed, both the brief stimulus light and a food pellet were delivered. This is a second order fixed ratio (FR) of 4 schedule with VR 16 components (FR 4 [VR 16:S]).

Once food-maintained responding was stable, each monkey was surgically implanted with an intravenous catheter under ketamine anesthesia (25 mg/kg/i.m.) using aseptic procedures. Eight to 10 days after surgery, monkeys were given access to alcohol during menstruation or the late luteal phase of the menstrual cycle.

Monkeys learned to self-administer alcohol intravenously on the same operant schedule of reinforcement used for food acquisition. An average of 64 responses was required for each food pellet or alcohol injection (0.12 g/kg/inj) under a second order schedule of reinforcement (FR 4 [VR 16:S]).

Food and alcohol each were available during four 1-hour sessions each day. Food sessions began at 11 a.m., 3 p.m., 7 p.m., and 11 p.m.; alcohol sessions at 12 noon, 4 p.m., 8 p.m., and 12 midnight. The conditions of food and alcohol availability and time out (when responses had no programmed consequence) each were associated with a colored stimulus light (S+) projected on a translucent Plexiglas response key. Each session lasted for one hour or until 65 food pellets or 20 alcohol injections were delivered. Complete details of the apparatus and basic operant paradigm used in our previous studies of drug self-administration have been published (Mello and Mendelson, 1978).

Alcohol self-administration data are reported for 30 menstrual cycles from six females. Since chronic high dose alcohol self-administration often resulted in amenorrhea (Mello et al. 1983), only cycles of average length which terminated in menstruation were selected for analysis. The average pre-alcohol control cycles and the alcohol self-administration cycles were not significantly different by t-test analysis.

Animal maintenance and research was conducted in accordance with the guidelines provided by the Committee on Laboratory Animals Facility and Care, the National Research Council Institute of Laboratory Animals Resources. The facility is licensed by the U. S. Department of Agriculture. The health of the monkeys was periodically monitored by a consultant veterinarian from the New England Regional Primate Center.

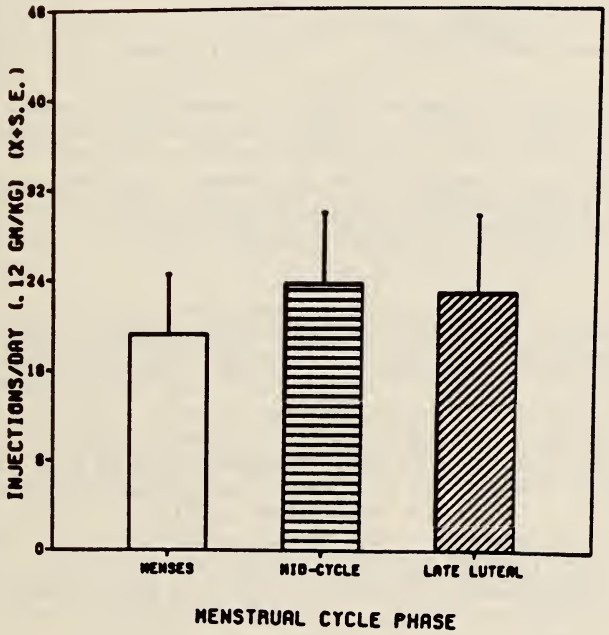
RESULTS

Thirty menstrual cycles were divided into four sub-groups according to the average dose of alcohol self-administered during each cycle. Only the low (0-1.5 g/kg/day) and moderate (1.5-3.0 g/kg/day) alcohol dose groups maintained normal menstrual cycles as indicated by a mid-cycle LH surge and subsequent rise in progesterone. Although the high intermediate (3.0-4.0 g/kg/day) and high (4.0-5.5 g/kg/day) dose groups had cycles that terminated in menstruation, analysis of pituitary and gonadal hormones indicated that these were not normal ovulatory menstrual cycles. Average daily alcohol doses above 3.0 g/kg consistently resulted in suppression of ovulation and luteal phase inadequacy as inferred from the absence of a mid-cycle LH surge and low basal levels of progesterone throughout the cycle.

The low dose group took significantly fewer alcohol injections at mid-cycle than during menstruation and the late luteal phase ($p < .01$). Exactly the opposite pattern occurred in the high-intermediate dose group. Monkeys self-administered more alcohol at

mid-cycle than during menstruation ($p < .001$) or the mid-luteal phase ($p < .05$). The high dose group self-administered more alcohol during both mid-cycle and the late luteal phase than during menstruation ($p < .01$) whereas the moderate dose group self-administered equivalent amounts of alcohol at each menstrual cycle phase.

Figure 1 shows the average number of alcohol injections self-administered during menstruation (days 1 through 5), at mid-cycle, and during the last 5 days prior to menstruation combined for all four dose groups. It is evident that alcohol self-administration was relatively constant across the menstrual cycle. There were no significant differences in the average number of alcohol injections per cycle phase, considered independently of dose as evaluated by t-tests for two means.



DISCUSSION

Alcohol self-administration by female rhesus monkeys did not co-vary systematically with menstrual cycle phase in a sample of 30 menstrual cycles. These data do not support the hypothesis, derived from clinical data, that alcohol self-administration increases at the premenstruum in comparison to other menstrual cycle phases (cf. Mello, 1980). There was no consistent tendency to increase or to decrease alcohol self-administration as a function of menstrual cycle phase.

Although alcohol-dependent rhesus monkeys develop derangements of reproductive function similar to those seen in alcoholic women (Mello et al. 1983), the temporal pattern of alcohol self-administration does not increase at the premenstruum in rhesus females as in alcoholic women (Podolsky, 1963; Belfer and Shader, 1976; Belfer et al. 1971). Other than those self-report data, there have been no direct observations of drinking patterns in women during the menstrual cycle on a clinical research ward, but these studies are currently underway in our laboratory. Parallel studies of the concordance of marihuana smoking with menstrual cycle phase in women also have failed to show increased drug use at the premenstruum (Mendelson, Personal Communication, 1984). However, until completion of studies of alcohol use patterns in human females using objective behavioral measures, the generality of these alcohol self-administration data in rhesus monkey cannot be evaluated.

At present, it is difficult to determine if the observed differences between rhesus monkeys and alcoholic women are primarily attributable to species differences, to methodological differences (observed behavior versus self-report measures) or to the impossibility of ascertaining the presence or absence of something analogous to a premenstrual tension syndrome in rhesus monkey. It does seem reasonable to conclude that the hormonal variations which define the menstrual cycle are not reliably associated with increases or decreases in alcohol self-administration in rhesus monkey.

In addition to clinical reports of increased drinking during the premenstruum, it has also been reported that women develop higher blood alcohol levels at the premenstruum than during menstruation or cycle days 13 through 18 (Jones and Jones, 1976a and b). These data seemed persuasive arguments that drinking patterns might be modulated by menstrual cycle phases (cf. Mello, 1980 for review). However, recent studies in human females failed to find differences in peak blood alcohol levels at the premenstruum, menstruation and cycle days 12 - 15 in nine women given sufficient alcohol to produce peak blood alcohol levels of 103 mg/dl (Hay et al. 1984). We also failed to find differences in blood alcohol levels following a standard dose of alcohol (1.5, 2.5 and 3.5 g/kg) in female rhesus monkey as a function of menstrual cycle phase (Mello et al. 1984b). The present report of stable alcohol self-administration patterns across the menstrual cycle is consistent with previous reports of stable blood alcohol levels following a standard dose of alcohol across the menstrual cycle (Hay et al. 1984; Mello et al. 1984b).

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Food Deprivation Produces Persistent Increases in Self-Administration Behavior During Cocaine Extinction

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INTRODUCTION

Drugs have been shown to maintain higher rates of self-administration behavior when they are presented along with exteroceptive stimuli that have acquired conditioned-reinforcing properties. When these stimuli are presented when the drug is not available, they facilitate responding that was previously rewarded by drug infusions (e.g., Goldberg, 1975). There are several areas of study suggesting that interoceptive changes may be as likely as exteroceptive changes to be associated with the reinforcing effects of drugs. For example, the presence or absence of food, liquid, or shock is discriminated by interoceptive changes produced by drug administration (Barry, 1974) and by food or water deprivation (Capaldi and Davidson, 1979). Interoceptive stimuli associated with intravenous infusions of saline and saline-dextrose infusions (Madden, Oei and Singer, 1980; Karoly, Winger, Ikomi and Woods, 1978; Schuster and Brady, 1964) or noncontingent drug infusions (DeWit and Stewart, 1981, 1983) facilitate responding that was previously rewarded by drug infusions.

The purpose of the present experiment was to examine the effect of interoceptive stimuli associated with food deprivation on drug-seeking behavior once drug access has terminated. Food deprivation markedly enhances the initiation and maintenance of drug-reinforced behavior (Carroll, 1982). This finding has been generalized across species, drug classes and routes of administration (Carroll and Meisch, 1984). Previous studies have also ruled out many possible explanations such as a general increase in activity or liquid intake, differential effects of food or no food in the stomach on absorption and distribution of the drug and anorexigenic effects of certain drug classes (Carroll and Meisch, 1984). However, mechanisms underlying food deprivation-induced increases in drug intake are unclear. The specific hypothesis that was tested in the present experiment was that interoceptive stimuli related to food deprivation become associated with the reinforcing effects of a drug, and these stimuli later function as conditioned reinforcers to elicit drug-seeking behavior.

METHODS

Animals

Twenty-three adult male Sprague-Dawley rats weighing between 450 and 520 g were used as subjects. The rats were divided into an experimental group (E) and four control groups (C-1, C-2, C-3 and C-4). All groups consisted of five rats except group C-1 which contained three rats. Each animal was implanted with an intravenous jugular catheter according to methods previously described (Carroll, France and Meisch, 1981). The rats were housed in a room with the temperature maintained at 25° C. They always had free access to water, and food availability was determined by the experimental procedure.

Apparatus

The rats were individually housed in octagonal operant chambers containing two levers (with lights above each) and a house light (Carroll et al., 1981). Responses on the left lever activated the lever light and an infusion pump for 5 sec delivering approximately 0.15 ml of saline or cocaine (0.1 mg/kg). Responses on the right lever were counted, and they activated the lever light for 5 sec, but they did not produce an infusion.

Procedure

After surgery, the rats were allowed to recover in the operant chamber for at least 48 hr. Subsequently, 24-hr sessions were run continuously for 41 consecutive days. At 10:00 a.m. data were recorded; trays, pumps, feeders and water bottles were maintained, and experimental conditions were changed. The experiment was divided into three phases: Training, Extinction and Testing. The procedures for the five groups differed only in the Training and Extinction phases (See Table 1). The experimental group (E) was given continuous access to cocaine infusions (0.1 mg/kg) under a fixed-ratio (FR) 1 schedule; that is, each infusion was contingent upon a lever press. All five rats began to self-administer cocaine after only a few hours in the operant chamber. During the Training phase, the rats were food satiated (S) or deprived (D) during successive 24-hr sessions according to the following 11-day sequence: S, S, D, S, S, D, S, S, D, S, S. During food satiation sessions, food was freely available; during food deprivation sessions, only 8 g of food was provided at the start of the session. At the start of the 10-day Extinction phase, saline was substituted for cocaine, and the rats were continuously food satiated. Throughout the subsequent 20-day testing phase, the rats continued to receive saline under an FR 1 schedule, and they were food deprived (8 g) every third day.

To evaluate the importance of food deprivation during the initial Training phase with cocaine, Group C-1 received the same training sequence as the Group E, except they were not food deprived. To determine whether the results of Group E could be attributed only to food deprivation experience during training, Group C-2 was treated as Group E except they received saline instead of cocaine during the Training phase. After recovery from surgery, this group was given brief exposure to cocaine self-administration in order to train the lever-press response and to generate an elevated rate of saline-maintained behavior that would be comparable to that of Group E. Cocaine was available until at least 25 infusions were obtained; this usually occurred within 24 hr. Food was freely available during this brief exposure to cocaine. Group C-3 was used to assess

the importance of the contingency between responding and cocaine infusions. This group received the same number of cocaine infusions as Group E over the 11-day Training phase, but infusions were not contingent upon upon lever-press responses; they were automatically programmed by a computer to be delivered according to the same pattern as Group E. Responses were counted, and they resulted in illumination of the lever light, but they did not result in infusions. Before the Extinction phase, in order to train the lever-press response, Group C-3 received access to cocaine under an FR 1 schedule until 25 infusions were obtained. Subsequently, saline was available under an FR 1 schedule for the Extinction and Testing phases of the experiment as in the other groups. Group C-4 was treated identically to Group C-3, except this group was food deprived (12g/day) during the 10-day Extinction phase in an attempt to extinguish the effect of stimuli associated with food deprivation.

Table 1. EXPERIMENTAL DESIGN

	Training Phase		Extinction Phase		Testing Phase	
Group	Infusions	Feeding Condition	Infusions	Feeding Condition	Infusions	Feeding Condition
Experimental	Cocaine, FR 1	S S D S S D S S D S S	Saline, FR 1	S S S S S S S S S S	Saline, FR 1	S S D S S D S S D S S D S S D S S D S S
Control 1	Cocaine, FR 1	S S S S S S S S S S S	Saline, FR 1	S S S S S S S S S S ·	Saline, FR 1	S S D S S D S S D S S D S S D S S D S S
Control 2	Saline, FR 1	S S D S S D S S D S S	Saline, FR 1	S S S S S S S S S S	Saline, FR 1	S S D S S D S S D S S D S S D S S D S S
Control 3	Cocaine, Yoked to Experimental group	S S D S S D S S D S S	Saline, FR 1	S S S S S S S S S S	Saline, FR 1	S S D S S D S S D S S D S S D S S D S S
Control 4	Cocaine, Yoked to Experimental group	S S D S S D S S D S S	Saline, FR 1	D D D D D D D D D D	Saline, FR 1	S S D S S D S S D S S D S S D S S D S S

RESULTS

Figure 1 shows substantial increases in cocaine-maintained responding and infusions during the Training phase. Responses on the activity lever did not differ as a result of the feeding condition. During the Extinction phase, responding declined to low levels; however, when food deprivation conditions were reinstated during the Testing phase, responding increased nearly seven fold. Group C-1 also showed decreased responding when saline was substituted for cocaine, but when they were food deprived during testing there were no increases in responding. Group C-2 showed a small gradual increase in saline-maintained responding throughout the three experimental phases, but there were no specific increases due to food deprivation. These results suggest that elevated responding due to food deprivation in the Testing phase was due to the specific combination of food deprivation and cocaine access during the Training phase. Group C-3 automatically received the same number of infusions as Group E during the Training phase; however, since infusions were not contingent upon responding, these rats responded at very low rates during the Training phase. When they were allowed one session of FR 1 access to cocaine after the Training phase, the group obtained a mean of 46.3 infusions within 1.2 sessions. When saline was

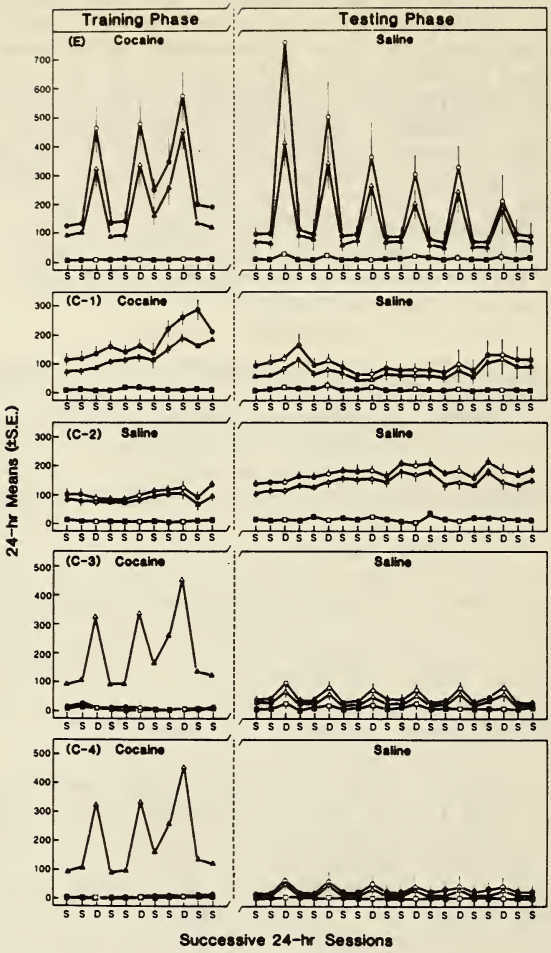

Figure 1. Effects of food satiation (S) and deprivation (D) on drug-lever responses (●), infusions (▲) and activity-lever responses (■). Points in the left frames represent 11 consecutive sessions of the Training phase. In Groups E and C-1 lever pressing was reinforced by cocaine (0.1 mg/kg); in Group C-2 lever-pressing was reinforced by saline, and in Groups C-3 and C-4 lever presses were counted but had no programmed consequences. The break along the abscissa represents a 10-day extinction period during which the rats received access to saline contingent upon lever-press responses (FR 1), and they were either food satiated (E, C-1, C-2 and C-3) or food deprived (C-4). During the Testing phase (right panels), all rats received FR 1 access to saline, and they were food deprived every third day. Each point represents a mean (± S.E.) of five rats except Group C-1 which consisted of three rats.

substituted for cocaine during the Extinction phase, there was an initial increase in responding for a day or two in some rats, but responding decreased and remained at low levels. During the Testing phase, responding remained low, but it nearly doubled during food deprivation sessions. There were no systematic differences in responding during the initial 10-day Extinction phase among the first four groups (E, C-1, C-2 and C-3); thus, the differences that occurred among these groups during the Testing phase were attributed to differing experimental conditions during the Training phase. The results of Group C-4 were mixed. Two of the rats responded in a manner similar to those in Group C-3. Response rates increased during food deprivation, but only during the first three food deprivation cycles. The other three rats showed no increase in saline-maintained responding during food deprivation. The results of this group indicate that when extinction (saline substitution) initially occurred while the stimuli associated with food deprivation were present, food deprivation was less likely to produce a high rate of saline-maintained responding than if extinction occurred during food satiation.

DISCUSSION

The results of this experiment indicate that the specific combination of drug-reinforced behavior and food deprivation produced a high rate of cocaine-reinforced behavior as well as a high rate of saline-maintained responding when the food deprivation condition was reinstated during the Extinction phase. During the Testing phase the probability of responding was increased such that if drug had been available, relapse behavior would have likely occurred. The control groups showed that food deprivation or a history of cocaine self-administration alone was not responsible for the reinstatement of high rates of behavior. Also, the contingency between lever-press responding and cocaine infusions was an important determinant of the result.

A tentative explanation of the current results is that interoceptive stimuli associated with food deprivation become paired with cocaine injection, and they come to function as conditioned reinforcers. The results of Group C-4 support this hypothesis. When stimuli associated with food deprivation were present throughout the 10-day Extinction phase, the ability of these stimuli to subsequently control self-administration behavior was substantially reduced. Similar results have been reported earlier in a comparison of the effects of presenting (or not presenting) exteroceptive drug-paired stimuli during extinction (Goldberg and Gardner, 1981). Subsequent reinstatement of the drug-related stimuli temporarily restored high rates and patterns of responding only when these stimuli had not been presented during extinction.

A problem with explaining the food deprivation effect by such a conditioning process is that i.v. drug intake increased during the first food deprivation session; there had been no specific previous pairings of food deprivation and drug effects. This suggests that conditioned increases in drug self-administration occurred almost immediately after the onset of the interoceptive effects of food deprivation. There are parallels for this type of rapid, one-trial learning in the taste aversion literature (Carroll and Smith, 1974; Domjan, 1977), whereby a pairing also exists between two interoceptive stimuli: ingestion of a substance

and an altered physiological state which can be produced by a variety of agents. A crucial variable for taste aversion learning is the novelty of the taste solution. Similarly, food deprivation is defined in the present study as a relatively novel condition for a free-fed laboratory animal. Thus, stimuli associated with food deprivation may be especially salient and easily paired with reinforcing effects of drugs.

An implication of the current results for the prevention and treatment of drug dependence is that internal stimuli, such as those associated with food deprivation, may contribute to the persistence and relapse of drug use. There are a few anecdotal reports of a relationship between fasting and an increased rate of drug dependence. For instance, a starvation study conducted during World War II revealed a substantial increase in the use of caffeine, nicotine and other substances in men maintained at reduced body weights (Franklin, Schiele, Brozek and Keys, 1948); the high rate of coca leaf chewing among the Quechua Indians of the Peruvian high plateau diminished when ordinary sparse diets were replaced by well-balanced meals, and returned when the sparse diets were resumed (Hanna and Hornick, 1977); and a higher than normal rate of drug dependence is reported among bulimic patients who intermittently fast and binge (Pyle, Mitchell and Eckert, 1981). Self-imposed fasting is also associated with the chronic use of some drugs such as amphetamine, cocaine and phencyclidine. These observations and the results from laboratory animal studies suggest that further research is needed to evaluate the role of food deprivation and other interoceptive events in the etiology of drug dependence.

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Parameters of Intracranial Self-Administration of Cocaine Into the Medial Prefrontal Cortex

N. E. Goeders and J. E. Smith

The neuronal substrates of cocaine reinforcement have been under investigation with pharmacological lesion, place-preference conditioning, and intravenous and intracranial self-administration procedures. Intravenous cocaine self-administration is attenuated by drugs that interfere with dopaminergic (DeWit and Wise 1977) and cholinergic (Wilson and Schuster 1973) neuronal activity, but enhanced with noradrenergic neuronal blockade (Goldberg and Gonzalez 1976). The locus of dopaminergic involvement has been suggested since 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens decrease intravenous self-administration (Roberts et al. 1980) without affecting heroin intake in the same animals (Pettit et al. 1982). These data suggest the dopaminergic innervations of the nucleus accumbens to be central to the processes mediating cocaine reinforcement. However, 6-OHDA lesions of this region do not attenuate cocaine place-preference conditioning (Spyraki et al. 1982), and the content of dopamine (DA) in the nucleus accumbens does not correlate with the degree of deficit seen in intravenous self-administration after similar lesions of the ventral tegmental region (Roberts and Koob 1982). Kainic acid lesions of this region which spare the dopaminergic innervations also decrease intravenous cocaine self-administration (Zito et al. 1983). These data suggest that multiple systems may be involved in the brain processes associated with cocaine reinforcement. Intracranial self-administration studies were initiated to determine the direct role of neuronal systems in cocaine reinforcement. Cocaine was found to be self-administered into the medial prefrontal cortex but not into the nucleus accumbens or ventral tegmental area (Goeders and Smith 1983). The parameters of this self-administration have been further investigated to determine the expanse of the potential site of action and the role of various neurotransmitter receptors.

Method

Adult male Fischer F-344 rats were initially stereotaxically implanted with 22-gauge guide cannulae into the medial prefrontal cortex (10.05 mm anterior, 0.6 mm from the midline and 2.1 mm below the surface of the brain; Konig and Klippel 1967). One group of rats was allowed to self-administer cocaine directly into the medial prefrontal cortex, while one group was given response-independent infusion of [^{3}H]-cocaine at a dose and schedule equivalent to the maximum rate of self-administration to determine the expanse of the potential site of action.

The drug was intracranially delivered with electrolytic microinfusion transducer systems (figure 1) that mount directly onto the guide cannulae using previously described procedures (Goeders and Smith, 1983; Goeders et al. 1984).

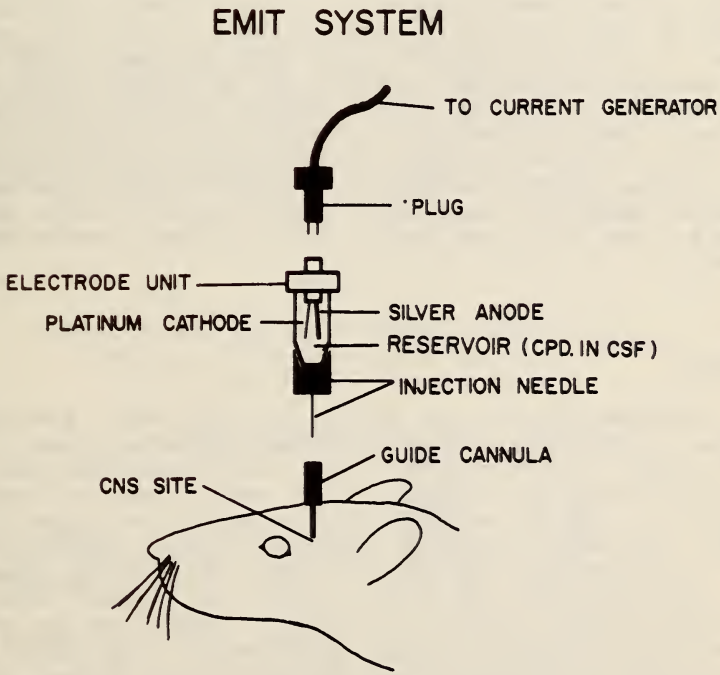

Figure 1. The electrolytic microinfusion transducer system used for intracranial administration and self-administration experiments (from Goeders et al. 1984) Copyright 1984, Ankho International Inc.

Radioactive Spread of [^{3}H]-Cocaine: Rats were given either 10, 20, or 40 (N=3 per condition) response-independent infusions of [^{3}H]-cocaine into this region on a random time 4-minute schedule which was equivalent to the maximum rate of self-administration. Each infusion contained 100 pmoles and 2,200 counts per minute of [^{3}H]-cocaine. Immediately following the last infusion, the animals were frozen in liquid nitrogen and the heads removed and stored at -70°C. The heads were warmed to -20°C, the brains removed, cut into 1 mm coronal sections and each section cut into 1 mm cubes using a eyepiece grid and stereomicroscope. Each tissue cube was placed in a counting vial, 100 ul of 0.1N NaOH added and stored overnight to dissolve the brain tissue. 100 ul of 0.1N HCl and 6 ml of scintillation cocktail were added to each vial and the radioactivity determined by liquid scintillation spectrophotometry.

Intracranial Self-Administration - Role of Neurotransmitter Receptors

Six rats were used to determine the role of cholinergic, dopaminergic and noradrenergic neurons in the intracranial self-administration into the medial prefrontal cortex. After stable baselines of self-administration (8-hr sessions every third day) were obtained and dose-effect relationships assessed, three rats were exposed in a random order to each of four drug conditions. Equimolar concentrations of atropine (cholinergic muscarinic antagonist), propranalol (alpha adrenergic antagonist), SCH 23390 (D_1 dopamine receptor antagonist) or sulpiride (D_2 dopaminergic receptor antagonist) were added to the cocaine injection solution and the intake and patterns of self-administration monitored.

Results

The self-administration of cocaine into the medial prefrontal cortex was dose-dependent and directed responding (Goeders and Smith 1983). The radioactive spread data demonstrates that the infused cocaine was localized in the medial prefrontal cortex (figure 2). At the maximum injection number and longest time point, sixty-seven percent of the total recovered radioactivity was located in the 1 mm cube containing the injection cannulae tip, with 93% within 1 mm of this site. This suggests that the self-administered cocaine is exerting its effects in the target area and not diffusing to other brain areas. Only 2.5% of the total infused radioactivity was recovered in the brain. Blood removed from the superior saggital sinus region did not show counts above background. This suggests cocaine is rapidly cleared from the injection site.

The neurotransmitter antagonists were either ineffective, had a direct effect or a delayed effect on cocaine self-administration (table 1). Sulpiride decreased the rate of self-administration

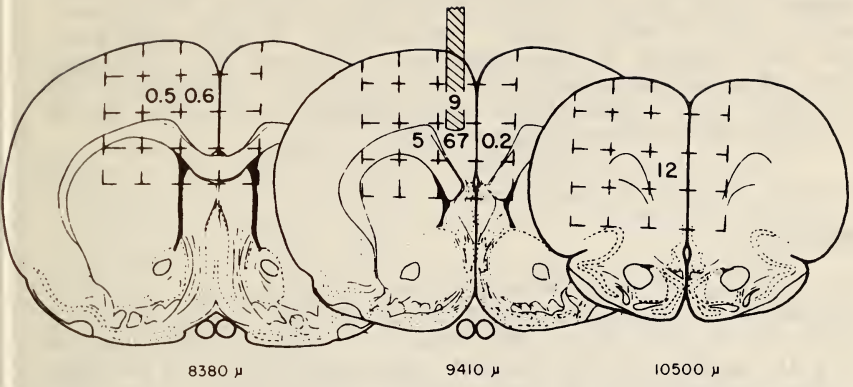

Figure 2. Location of [^{3}H]-cocaine infused into the medial prefrontal cortex at a rate equivalent to the highest rate of self-administration. The values represent the percent in that 1 mm cube of the total radioactivity recovered in the brain. Values are means for three animals. Standard deviations were omitted for space limitations but were 10-15% of each mean.

Table 1

Percent of Baseline Cocaine Interinfusion Intervals for the Intracranial Self-Administration of Cocaine Plus Equimolar Concentrations of Each Antagonist

	Percent of Baseline Interinfusion Intervals			
Antagonist	Baseline	Day of	First Post-Treatment Session	Second Post-Treatment Session
Atropine	100 ± 14	99 ± 1	160 ± 9†	100 ± 14.3
Propranalol	100 ± 27	106 ± 28	98 ± 14	85 ± 5
SCH 23390	100 ± 13	123 ± 29	177 ± 13†	121 ± 8
Sulpiride	100 ± 10	319 ± 83†	464 ± 280	112 ± 74

Values are means ± standard deviations for N=3. Significance of the differences determined with Student's t-tests were: †$p<0.01$.

that was consistent with patterns of intake seen when the dose was lowered from the optimum level. This effect was still seen three days later, but had disappeared by the second post-drug session (6 days). Atropine and SCH23390 did not have a direct effect on the day of administration but did on the first post-drug session (3 days later). The patterns of self-administration were similar to those seen when the dose was increased. These effects dissipated by the next session. Propranalol had no effect on self-administration. Phenoxybenzamine was tested in one animal and also had no effect.

Discussion

The intracranial self-administration of cocaine into the medial prefrontal cortex is the result of the actions of the drug at a small site at the tip of the injection cannulae. The injected drug is rapidly cleared from this site, resulting in a decrease in the concentration at the receptor subpopulation initiating the reinforcing properties resulting in the stimulus that leads to the next infusion. Dopaminergic D_2 receptors appear to be directly involved in the initiation of these reinforcing properties, while muscarinic cholinergic, alpha adrenergic, beta adrenergic, and D_1 dopaminergic receptors are not. However, the D_1 and muscarinic cholinergic receptors appear to be indirectly involved since blockade results in a delayed effect that resembles increasing the dose of cocaine. The role of serotonergic and GABAergic receptors is currently being assessed. These data suggest several possible synaptic receptor configurations at the self-administration site that may have general implications in brain reinforcement processes.

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Evaluation of Intramuscular Meptazinol and Morphine in Cancer Patients With Postoperative Pain

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Development of analgesics with the effectiveness but not the undesirable effects of morphine has prompted evaluations of selected agonist-antagonist analgesics. Meptazinol, m-(3-ethyl-1-methyl-hexa-hydro-1H-azepin-3-yl) phenol HCl, is one of these. Since initiation of evaluations in 1975, there have been reports of its use in pain of obstetrics (Nel et al. 1981; Nicholas and Robson 1982); renal colic (Robson 1983); surgery (Cohen et al. 1983; Dos Santos-Pereira 1980; Gibbs and Johnson; Hedges et al. 1980; Moyes et al. 1979; Paymaster 1976; Paymaster 1977; Paymaster 1983; Saviano et al. 1980; Slattery et al. 1982; Verschraegen and Rolly 1979); cancer (Staquet 1978); myocardial infarction (Sonecha et al. 1983); and other indications (Coutinho 1982). It has been compared with other drugs, including buprenorphine (Harmer et al. 1983), meperidine (Harmer et al. 1983; Hedges et al. 1980; Nel et al. 1981; Nicholas and Robson 1982; Paymaster 1977; Paymaster 1983; Slattery et al. 1981), morphine (Cohen et al.1983; De Rosayro et al. 1981; Harmer et al. 1983), omnopon (Moyes et al. 1979), and pentazocine (Paymaster 1977; Staquet 1978; Verschraegen and Rolly 1979). Reviews indicate that IM meptazinol differs from IM morphine: a relative potency in the range of 1/10, a faster onset and shorter duration of analgesia, a lower abuse potential, and different side effect profile (Robson 1982; Stephens et al. 1978). Meptazinol is reported to produce less respiratory depression (Jones 1983; Jordan et al. 1979; Jordan et al. 1979; Slattery et al. 1983; Slattery et al. 1982), and to have benign effects on the cardiovascular system (Budd 1976; Camu and Rucquoi 1983; DeRosayro et al. 1981; Moyes et al. 1979; Paymaster 1977). It also has been reported to produce a low occurrence of CNS side effects (e.g., euphoria, restlessness, hallucinations, dysphoria)(Evans et al. 1983; Robson 1983) and constipation (Stephens et al. 1978), although nausea and vomiting are not uncommon (Nicholas and Robson 1982; Paymaster 1976; Richens et al. 1983; Stephens et al. 1978). It has also been suggested that meptazinol is unique in being a mu-1 receptor selective opioid analgesic (Spiegel and Pasternak 1984).

Previous clinical studies were primarily efficacy evaluations and do not provide valid estimates of relative potency. The primary

objective of this study was to determine the analgesic potency of IM meptazinol relative to morphine in moderate to severe postoperative pain. Secondary objectives were to assess side effects and effects on selected aspects of mood.

METHODS

Methods adhered to the principles of design and procedure previously reported (Houde et al. 1960; Wallenstein and Houde 1975). Patients were seen hourly, with an additional observation at 1/2 hr following study drug, by a nurse-observer who recorded reports of pain, relief, and mood. At the time of study drug and at 2 hrs, patients also completed an adaptation (Kaiko et al.1981) of a mood questionnaire (Lasagna et al. 1962). Concomitant signs and symptoms and volunteered side effects were also recorded. Observations were continued for 6 hrs or until baseline pain returned. The assay consisted of equi-log-spaced doses of IM meptazinol (50,100 and,200 mg) and morphine (4,8, and 16 mg). Each patient received 2 study treatments, each on a different day: a lower dose of one drug and an upper of the other, or the middle dose of each on a double-blind, randomized basis, and balanced for order. Analyses of variance for twin-crossover assay (Finney 1964) were employed.

RESULTS AND DISCUSSION

The completed assay incorporated 102 completing patients and 26 patients who dropped out. Table 1 summarizes the results of the relative potency calculations. In terms of peak effects, 120 to 155 mg meptazinol is equianalgesic with 10 mg morphine; in terms of total effects, 175 to 245 mg of meptazinol is equianalgesic to 10 mg of morphine. The difference in peak and total equianalgesic doses indicates that meptazinol provides a shorter duration of analgesia for a given peak effect. At comparable peak effects as provided by morphine, meptazinol provides peak relief at less than 1 hr in comparison to between 1 and 2 hrs following morphine. The faster onset is accompanied by a shorter duration of action (Table 2).

Table 3 details the significant changes between baseline and 2 hrs in terms of the contrasting mood words for each study treatment. Only morphine provided significant mood improvements and in a dose-related manner. Meptazinol provided only for a few significant changes and these were toward negative feelings. In terms of analgesia at 2 hrs (not shown) 100 mg meptazinol is equivalent to 4 mg morphine and 200 mg meptazinol is equivalent to 8 mg morphine.

The percentage of patients with side effects (Table 4) was dose-related for both drugs and in a comparable range, but with a steeper slope following meptazinol. When occurrence is expressed in terms of the number of effects, it becomes apparent that meptazinol results in more side effects except at the 50 mg dose. Most common to morphine (Table 5) was sleepiness followed far behind by grogginess, dry mouth, and sweating. Most common to meptazinol was nausea, followed closely by sweating, sleepy, and dizzy. There were more reports of side effects exclusive to meptazinol than to morphine,

TABLE 1. Mean IM meptazinol milligram dosages (with 95% confidence intervals) equianalgesic with 10 milligram of IM morphine.

ESTIMATE OF ANALGESIA	PEAK		TOTAL	
Pain intensity decrease	Mean	95% C.I.	Mean	95% C.I.
Categorical	120	(80-170)	175	(125-270)
"Tursky"	140	(90-215)	190	(130-310)
Visual analog	150	(95-240)	180	(115-305)
Pain relief				
Categorical	155	(105-245)	225	(155-400)
Visual analog	155	(105-245)	245	(160-455)

TABLE 2. Mean (SE) time (hr) to peak analgesia (visual analog pain relief) and to remedication following IM morphine and meptazinol.

Morphine	PEAK TIME			REMEDICATION TIME	
4 mg	1.1	(0.14)	.....	3.6	(0.52)
8 mg	1.3	(0.17)	.....	4.7	(0.37)
16 mg	1.8	(0.22)	.....	6.2	(0.84)
All doses	1.4	(0.11)	.....	4.8	(0.36)
Meptazinol					
50 mg	0.87	(0.11)	.....	3.1	(0.24)
100 mg	0.96	(0.16)	.....	3.7	(0.39)
200 mg	0.87	(0.10)	.....	4.1	(0.50)
All doses	0.94	(0.07)	.....	3.6	(0.22)

TABLE 3. Significant (P<0.05) changes (0 to 2 hr) in selected aspects of mood following IM morphine and meptazinol.

CONTRASTING PAIRS		Morphine			Meptazinol	
-	+	4 mg	8 mg	16 mg	100 mg	200 mg
Shaky	Serene		0.66	1.13		
Restless	Peaceful		0.97	1.10		
Nervous	Calm			1.06		
Alone	Sociable	0.97	0.63	1.03		
Serious	Amused	0.85		0.97		
Uneasy	At ease			0.90		
Heavy	Buoyant		0.55	0.81	-0.57	
Blue	Cheerful			0.77		
Apathetic	Enthusiastic			0.71		-0.90
Sad	Happy			0.71		
Pessimistic	Optimistic				-0.60	

TABLE 4. The occurrence of side effects (SE) following IM morphine and meptazinol in moderate to severe postoperative pain.

Dose	Morphine			Meptazinol		
	4 mg	8 mg	16 mg	50 mg	100 mg	200 mg
No. administrations	37	45	34	39	39	37
No. with SE	12	22	22	7	19	27
Percentage with SE	32%	49%	65%	18%	49%	73%
No. of SE reports	19	32	58	12	59	129
No. of SE/patient	0.51	0.71	1.71	0.31	1.51	3.48

and among these were some particularly disturbing effects.

In conclusion, relative to IM morphine in moderate to severe pain in postoperative cancer patients: a) 120 to 155 mg of IM meptazinol is equivalent to 10 mg of IM morphine in terms of peak analgesic effects; meptazinol provides a more rapid onset and a shorter duration of analgesia, such that 175 to 245 mg of meptazinol is equivalent to 10 mg of IM morphine in terms of total analgesic effects; b) while morphine improves selected aspects of mood in a dose-dependent manner, meptazinol has a negligible or negative effect on mood; c) side effect occurrences are dose-related and particularly disturbing in about 15% of patients following doses of meptazinol which are equianalgesic with commonly employed doses of IM morphine for moderate to severe pain; d) for a given degree of analgesia, the overall effects of meptazinol are less satisfactory than those of morphine. The latter conclusions are in apparent contradiction to those of many previous reports. In reviewing that literature, and in examining our patient sample for characteristics which might be associated with such differences, our tentative explanation for the differences lies in the fact that previous studies rarely extended the dose of IM meptazinol beyond 100 mg.

TABLE 5. Side effect profile of IM morphine and meptazinol

Exclusive to Morphine (13 pts.)		Common to both drugs:	MS	MEP	Exclusive to Meptazinol (20 pts.)	
Disoriented	2	Sleepy	38	20	Feels faint	5
Apathetic	1	Groggy	7	5	Tachycardia	1
Feels sad	1	Dry mouth	6	5	Hypotension	1
Crying	1	Relaxed	4	1	Pale	1
Itching	1	Feels Jumpy	4	2	Pressure in stomach	4
Palpitations	1	Headache	3	2	Tightness in throat	1
Ear pressure	1				Frightened	3
Constricted pupil	1	Inj. pain	2	2	Loss of control	2
Dyspepsia	1	Irritable	1	1	Ominous feeling	1
					Warm	4
		Nausea	5	25	Flushed	2
		Sweating	6	24	Hot flashes	1
		Dizzy	3	19	Hypertension	1
		Vomiting	2	10	Nervous	1
		Stom. cramps	2	3	Restless	1
		Lightheaded	1	9	Respiratory depress.	1
		Floating	1	7	Numbness and tingling in face	1
		Weak	5	7		
		Blurred vis.	2	6	Lips feel numb	1
		Feels hot	3	5	Numbness in arm	1
		Shaky	1	3	Eyes big for sockets	1
		Vis. halluc.	1	2	Eyes tearing	1
					Eyelids feel puffy	1
					Rhinorhhea	1
					Nose congested	1
					Diarrhea	1
					Difficulty sleeping	1
					Slurred speech	1

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Analgesic Efficacy of Intramuscular Flunixin Meglumine Compared to Meperidine: A Preliminary Report

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Flunixin is an aniline derivative of nicotine acid with analgesic, antipyretic, and anti-inflammatory properties. In animal models, flunixin meglumine, the n-methyl glucamine salt, was found to be essentially bioequivalent to flunixin in terms of pharmacologic activity and absorption characteristics when given orally. However, its analgesic potency was much greater than that of flunixin by the subcutaneous and intramuscular routes. This finding appears to be related to the faster absorption of the salt compared to the free acid. In the same animal models flunixin meglumine given by these routes was generally more potent than meperidine, codeine and pentazocine, and comparable to morphine.[4]

The present clinical trial was, to the best of our knowledge, one of the first to be conducted to assess the analgesic efficacy of flunixin meglumine in man. Our objective was to evaluate single, parenteral doses of 20, 40, and 80mg of flunixin, compared to 50 and 100mg of meperidine and placebo when administered to hospitalized patients for the control of moderate to severe pain following various gynecological surgical procedures.

METHODS

The study was a double-blind, parallel group, single-dose design. Patients who were able to communicate meaningfully with the nurse-observer and who gave written informed consent to participate in the study were considered. Patients were included in the trial if they had either moderate or severe pain secondary to cesarean section or gynecological surgery which required treatment with a parenteral analgesic. All subjects were between eighteen and seventy-five years of age. Patients were excluded if they were breastfeeding, had any complicating illness, or had received any other investigational drug within 4 weeks prior to enrollment in the study. Patients with a history of drug dependence or known allergic sensitivities to the test medications were also excluded.

Patients were stratified according to moderate or severe baseline pain and were then randomly assigned to receive either placebo, meperidine 50 or 100mg, or flunixin meglumine 20mg, 40mg, or 80mg.

When the patient's pain intensity was either moderate or severe, study medication was administered by the nurse-observer. The same nurse-observer interviewed the patients at the time the medication was administered at a half hour, one hour and hourly thereafter for four hours. If the patient was asleep at a scheduled interview time, she was awakened. At each observation, the patient was asked to assess the intensity of her pain, and also to classify her degree of pain relief. If a patient reported inadequate pain relief before the first hour, a conventional analgesic was given and she was removed from the study. If a patient was remedicated with a conventional analgesic after the first hour she was included in the statistical analysis. At the completion of the study, patients were also requested to give their global evaluation of the study medication.

The statistical analysis utilized standard methodology[3]. Several summary measures of analgesia were derived from the interview data. Pain Intensity Difference (PID) is the difference between the pain intensity score at an observation point and the baseline intensity. SPID is the sum of the hourly PID scores, weighted by the time interval between observations, and is an estimate of the area under the time-effect curve. The variable TOTAL is the sum of the hourly relief values, also weighted by the length of the time interval between observations. A comparison was made among the six treatments using a one-way analysis of variance (ANOVA) to test the hypothesis of no difference between treatments for all parameters[2]. If the ANOVA was significant at the 0.05 level, tests were performed to investigate pairwise differences between treatments using Peritz' modification of the Neuman-Keuls procedure.[1]

RESULTS

One hundred and ninety patients were entered in the study and all are included in this preliminary report. Each of the treatments was given to a group of 30 to 32 patients. Mean scores for the various measures of analgesia and significant treatment differences are described in Table 1, and time-effect curve for PID is shown in Figure 1. All three doses of flunixin and meperidine 100mg differed significantly from placebo on many hourly and summary parameters. Meperidine 50mg was significantly more effective than placebo only at the half-hour and one-hour readings. After the second hour, there was a decrease in the level of analgesia for meperidine whereas flunixin remained effective throughout the entire period of observation. At the later hours, flunixin 80mg was statistically more effective than both doses of meperidine. For SPID, TOTAL, Time to Peak and the global assessment of study drug, all active drugs were significantly more efficacious than placebo with the exception of meperidine 50mg which, for some of the variables was not significantly different from placebo. The average of the responses of the three doses of flunixin was superior to the average of the two doses of meperidine for the third and fourth hour variables, SPID, and TOTAL, but was inferior at the half-hour reading. Relative potency and dose response analyses are in progress and will be reported at a later date.

Thirty patients reported adverse effects. The most frequently reported adverse effect with the three flunixin treatments was pain or discomfort at the injection site, while with the meperidine treatments dizziness and sweating were more frequently reported. In addition, one patient who received 50mg meperidine reported difficulty breathing and a sharp pain in the thorax area. Two patients who received placebo also complained of pain at the injection site.

DISCUSSION AND CONCLUSION

Flunixin 20, 40 and 80mg and meperidine 100mg were all found to be effective analgesics. Flunixin 80mg was significantly more effective than meperidine 50mg for several analgesic measures including SPID and TOTAL. In addition, flunixin 80mg was significantly better than meperidine 100mg at the fourth hour. Flunixin 20 and 40mg was significantly better than meperidine 50mg for several variables, particularly for those of the third and fourth hours.

Globally flunixin 80mg at half-hour is less effective than 100mg of meperidine, at one-hour it is approximately equivalent and thereafter has a higher mean effect. The 20 and 40mg doses have mean responses similiar to meperidine 100mg. During the third and fourth hours, there were statistically significant differences for all doses of flunixin in comparison to meperidine.

The availability of a non-steroidal anti-inflammatory drug for parenteral administration with efficacy in the range and possibly more effective than meperidine has many advantages. It makes available a potent analgesic which is a non-narcotic, a non-respiratory depressant, a non-inhibitor of cough, and non-sedating. It would be advantageous in clinical use for patients with pulmonary insufficiency and patients in the immediate post-operative condition where cough and respiratory depression may be a problem.

In summary, the flunixin, a non-steroidal anti-inflammatory drug is an effective parenteral analgesic that has a role to play in clinical situations requiring analgesics of strengths equivalent to meperidine.

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TABLE I. Measures of Analgesic Efficacy

Variable	Placebo N=32	Meperidine 50mg N=30	Meperidine 100mg N=32	Flunixin 20mg N=32	Flunixin 40mg N=32	Flunixin 80mg N=32
Pain Intensity Differences (PID)						
1/2 hour	0.56	1.14 P	1.38 P	1.03 P	1.06 P	0.97 P
1 hour	0.72	1.24 P	1.50 P	1.38 P	1.41 P	1.64 P
2 hours	0.75	1.10	1.44 P	1.50 P	1.38 P	1.76 P
3 hours	0.72	0.86	1.13	1.53 P,M	1.53 P,M	1.70 P,M
4 hours	0.66	0.48	0.69	1.25 P,M,H	1.25 P,M,H	1.49 P,M,H
SPID	2.77	3.64	4.69 P	5.48 P	5.39 P	6.24 P,M
TOTAL	4.23	5.69	7.22 P	8.25 P	8.19 P	9.46 P,M
Time to Peak	121.90	84.80	55.30 P	71.30 P	76.90 P	74.50 P
Global Evaluation of Test Drug	0.97	1.45	1.75 P	1.84 P	1.69 P	2.00 P

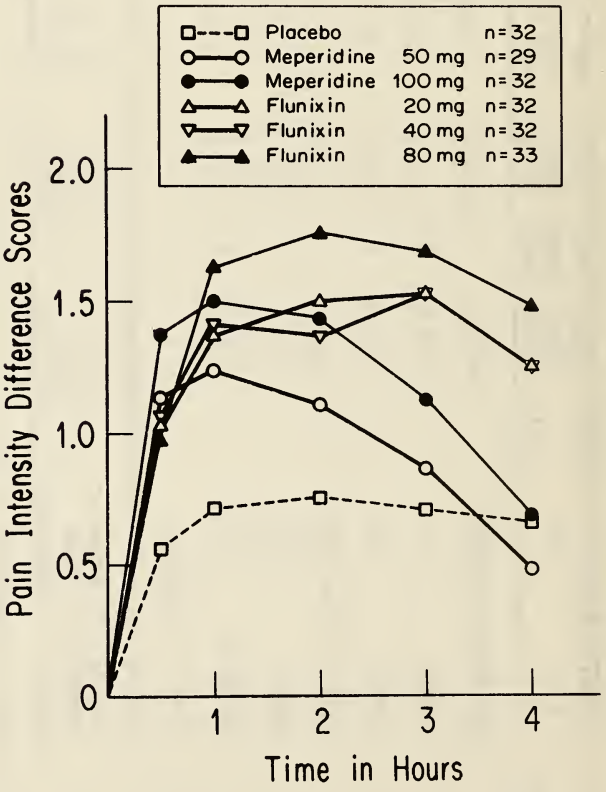
P=Significantly more effective than placebo, $p \leq 0.05$
M=Significantly more effective than meperidine 50mg, $p \leq 0.05$
H=Significantly more effective than meperidine 100mg, $p \leq 0.05$

TABLE II. Incidence of Adverse Effects

Adverse Effects	Placebo N=32	Mep 50mg N=30	Mep 100mg N=32	Flu 20mg N=32	Flu 40mg N=32	Flu 80mg N=32
Difficulty Breathing		1				
Dizzy		2	6			1
Drowsy			1			
Injection Site Pain	2			3	4	3
Sleepy						1
Sweating		3	2	3		1
Thorax Discomfort		1				
No. of Pts. Reporting Adverse Reaction	2	5	8	5	4	6

Mep = meperidine
Flu = flunixin

Figure 1: Time effect curve for mean PID scores are calculated by subtracting the mean pain intensity score for each observation point from the pain intensity at 0-hour.



Three-Choice Discrimination in Methadone Maintenance Patients: Hydromorphone, Naloxone, and Saline

Kenzie L. Preston; George E. Bigelow; Maxine L. Stitzer; and Ira A. Liebson

Recent data indicate that drugs acting at the various opioid receptors produce discriminable stimulus effects which make it possible to use behavioral drug discrimination testing procedures as a basis for classifying drugs with respect to the similarity of their pharmacological actions. It has been demonstrated that a number of infrahuman species can not only reliably discriminate opioid drugs from saline over a range of doses but also can discriminate between opioid drugs which act at different opioid receptors (for review see Herling and Woods, 1981). Although a two-choice discrimination (drug vs. placebo) is the more frequently used methodology, a three-choice discrimination (drug 1 vs. drug 2 vs. placebo) has also been successfully used to study opioid stimulus effects. The results of these three-choice discrimination studies were compatible with findings in other animal studies using a two-choice discrimination paradigm (White & Holtman, 1983).

The purpose of the present study was to develop drug discrimination procedures for use in human volunteers. Although subjective effect measures such as true/false questionnaires, adjective rating scales, and questionnaires concerning similarity of a test drug to previously used street drugs have been very useful in describing the effects of various drug classes, it appears likely that a drug discrimination paradigm could be successfully combined with the collection of these traditional subjective effect measures to obtain finer and more complete descriptions of the subjective effects of psychoactive drugs. The addition of drug discrimination to human behavioral pharmacological studies could provide direct comparison of the effects of study drugs to standard drugs with less dependence on each subject's own unknown and unique street drug history.

In this initial pilot study we trained methadone maintenance volunteers in a three-way drug discrimination procedure to discriminate between the effects of saline, hydromorphone, and naloxone—i.e., between no pharmacological effect, an opioid/mu-agonist effect, and a withdrawal/mu-antagonist effect. Following this discrimination training dose-effect functions were determined for the two active training compounds.

METHODS

Subjects: The participants were three adult male methadone maintenance patients who gave written informed consent and who were paid for their participation. The subjects reported prior narcotic addiction of 12 to 16 years duration and participation in a methadone maintenance program for two to eight years. The subjects lived on an eight-bed inpatient research unit throughout their participation in the study. Two subjects were maintained on methadone hydrochloride 50 mg daily, the third subject on 40 mg daily; methadone doses were given at 6:00 p.m. daily.

Drugs: The training drugs were saline (0.5 ml), hydromorphone HCl 10 mg, and naloxone HCl 0.15 mg. Hydromorphone powder (Knoll Pharmaceuticals) was dissolved in bacteriostatic saline to the desired concentration; naloxone 0.4 mg/ml (Endo) was diluted to the desired concentration with bacteriostatic saline. Doses were given in a volume of 0.5 ml intramuscularly. Doses of each drug are expressed in terms of the salt. Training drugs were identified to subjects only by arbitrary letter codes. For each subject these drug letter codes were randomly determined, but remained unchanged throughout the protocol. Drug was administered under double-blind conditions.

General Methods: The study proceeded in three phases: Training/Acquisition, Test of Acquisition, and Test Drug Discrimination. Discrimination training was conducted on sessions 1-6, during which the subject received, in random order, 2 sessions of exposure to each of the two active training drugs and to placebo. During these training exposures each drug was identified to the subject by letter code prior to drug administration. The subject was instructed to attend carefully to the drug effects and to try to discriminate precisely among them; he was informed that in each session he would be able to earn money by correctly identifying the administered drug by letter code. In sessions 7-12 acquisition of the discrimination was tested by exposing the subject in randomized block order to the training doses of each of the three training compounds to determine whether the subject could correctly identify them by letter code. In these test-of-acquisition sessions the subject received feedback about the code of the administered training drug after the session. This test-of-acquisition procedure was also repeated between test sessions during the subsequent testing phase to insure continued correct discrimination. Beginning with session 13, a series of test sessions was conducted on alternate days, separated by one test-of-acquisition session in which one of the training drugs was given. During this testing phase four doses of each active training drug (including the training dose) and saline were tested twice each in randomized block order. Following each test session the subject did not receive feedback of the correct drug identification. All 3 subjects completed the protocol through session 12. One subject completed the entire study protocol.

Experimental Session: A TRS-80 Model I microprocessor, located in an experimental room, was programmed to present all questionnaires in a prearranged and timed sequence, store the subject's responses, and print a data output following each session. At the beginning of each

experimental session, the subject completed the subjective report forms. The scheduled drug was then administered. During the initial training sessions the subject was informed of the drug's identifying letter code at the time of injection. The subject remained under observation for ten minutes and then completed the post-drug discrimination and subjective effect testing. Post-drug testing lasted for one hour and consisted of 3 repeating 20-minute cycles followed by a final subjective effect form. At the end of test-of-acquisition sessions a sealed envelope was opened, and the staff informed the patient of the letter-code identity of the administered drug; following test sessions the card said only that the session had been a test session and that the identity of the drug could not be revealed.

Discrimination Procedures: Drug discrimination data were collected in three ways. In each procedure only correct responses were converted to monetary reinforcement for the subject. As one component of each assessment cycle the subject made a discrete choice, naming by letter code (A, B, or C) the drug he thought he had received. A second component asked the subject to distribute 50 points between one or more of the three drug choice alternatives depending upon how certain he was of the identity of the administered drug. In a third component the subject responded on a fixed interval 1 sec schedule on computer keys designated with drug letter codes to earn points. During each 8.5-minute operant responding component, points could be earned for each of the 3 choice drugs by pressing the key corresponding to that drug; however, a 10-sec delay occurred whenever the subject switched from one key to another (a change-over delay, used to discourage ill-considered switching among alternatives).

Subjective Effect Measures: Subjective effect measures included: (1) the 49-item Addiction Research Center Inventory (ARCI) Short Form, which contains the MBG scale ("euphoria"), the LSD scale ("dysphoria") and the PCAG scale ("sedation"); (2) a 32-item adjective rating scale containing an opioid agonist scale (to detect opioid-like effects) and an antagonist scale (to detect opioid withdrawal-like effects), which the subject rated on a 5-point scale from 0 (no effect) to 4 (maximum effect); (3) quantitative visual analog scales to indicate the degree of drug effects, drug liking, "good" and "bad" effects, and subjective "high" on a scale from "not at all" to "extremely".

Data Analysis: The results of the discrimination training (discrimination of the training doses following two exposures to each training drug) are reported as mean percent correct identifications from sessions 7-12. The results of the subjective effect measures are reported as the mean of overall scores (average from four exposures to each drug in sessions 1-12) for each individual subject; mean change from pre-drug scores is reported for ARCI scales and adjective checklist scales. A repeated measures analysis of variance (ANOVA) was conducted, and Duncan's multiple range test was performed where appropriate. Effects were considered statistically significant if $p < 0.05$.

RESULTS

The results from the discrimination training and test of acquisition trials for the three subjects enrolled in this portion of the study are shown in Table 1 and 2. The discrimination between the three training drugs was readily learned, and few errors were made in identifying the training doses during the test of acquisition sessions (7-12). Table 1 shows percent correct identifications for each of the three drugs for each of the three discrimination measures. Naloxone 0.15 mg was most consistently correctly identified. The results of the three discrimination measures were similar for each drug.

Table 1

Percent Correct Identifications in the Discrimination Measures for Test of Acquisition Trials

	Hydromorphone	Saline	Naloxone
Discrete Choice	75.0 (11.8)	73.6 (12.0)	93.3 (5.4)
Point Distribution	75.0 (11.8)	73.6 (12.0)	93.3 (5.4)
Operant Responding	76.6 (11.8)	85.5 (5.8)	93.3 (5.4)

Standard errors are given in parentheses, N = 3

Table 2

Results of Subjective Effect Measures from Training and Acquisition Trials

	Hydromorphone	Saline	Naloxone
Visual Analogue Scales[1]			
Drug Effect (Strength)	39.6 (13.2)	5.9 (4.7)	58.7 (11.3)
Liking	67.5 (0.3)*	0.8 (0.5)	0.9 (0.6)
Good Effects	64.4 (9.9)*	1.9 (1.5)	0.2 (0.1)
Bad Effects	0.0 (0.0)	4.9 (4.0)	73.5 (6.1)*
High	37.4 (15.2)	0.9 (0.7)	0.0 (0.0)
Adjective Rating Scales[1]			
Agonist (Morphine-like)	16.7 (2.3)*	-3.7 (2.3)	6.3 (3.0)
Antagonist (withdrawal-like)	-0.6 (1.4)	1.3 (1.1)	20.8 (0.5)*
Addiction Research Center Inventory[2]			
MBG Scale (euphoria)	5.9 (1.4)*	-0.5 (0.5)	-0.9 (0.8)
PCAG Scale (sedation)	-1.6 (2.0)	0.4 (0.3)	3.1 (0.5)
LSD Scale (dysphoria)	-1.1 (0.2)	0.4 (1.1)	3.4 (1.4)

Standard errors are given in parentheses. * - significantly different from saline, $p < 0.05$, 2-tailed Duncan's Multiple Range Test. 1 = 30 min post injection. 2 = 70 min post injection.

The results of the measures of subjective effects produced by the training drugs in sessions 1-12 are shown in Table 2. Significant treatment effects were produced on three of the five visual analog scales: "liking" [$F(2,4) = 32.4$, $p = 0.005$], "good effects" [$F(2,4) = 25.5$, $p = 0.007$]. and "bad effects" [$F(2,4) = 66.1$, $p = 0.002$]. Hydromorphone produced significantly greater "liking" and "good effects" scores than both saline and naloxone, while subjects reported significantly greater "bad effects" for naloxone than for saline and hydromorphone. The results of the adjective checklist agonist and antagonist scales also showed significant treatment effects: agonist scale [$F(2,4) = 12.9$, $p = 0.02$] and antagonist scale [$F(2.4)$, 97.2, $p = 0.001$]. Hydromorphone significantly increased agonist scale scores compared to saline; naloxone significantly increased antagonist scale scores compared to saline and hydromorphone. Two scales from the Addiction Research Center Inventory showed significant effects of treatments: LSD scale [$F(2,4) = 7.2$, $p = 0.048$] and MBG scale [$F(2,4) = 8.6$, $p = 0.037$]. Naloxone produced significantly greater scores on the LSD scale than did hydromorphone. Hydromorphone significantly increased MBG scale scores compared to both saline and naloxone. Naloxone also produced an increase in the PCAG scale, though this effect did not reach significance.

Dose effects functions for hydromorphone and naloxone on discrimination measures and subjective effects measures have been determined in one subject thus far. Orderly dose response functions for the discrimination of both hydromorphone and naloxone resulted with all three discrimination components. Figures 1 and 2 show the results from the operant responding discrimination measure. Saline was correctly identified in all test of acquisition trials in which it was presented. Hydromorphone 2.5 and 5.0 mg produced 40 to 50% correct identifications while the training dose (10 mg) and 14 mg produced 100% correct identifications. Naloxone 0.037 mg was identified as saline in each presentation; naloxone 0.075 mg was identified as being naloxone in 50% of the identifications. Naloxone 0.15 mg (the training dose) and 0.20 mg produced 100% identifications as naloxone.

The two active test drugs also produced similar (but complementary and contrasting) orderly dose-dependent effects upon the various subjective report measures. The results also agree with those found in the discrimination training and test of acquisition sessions reported above for three subjects. Hydromorphone produced dose-dependent increases in visual analog scale ratings of "drug effect", "good effects" (Figure 1), "high", and "liking". Virtually no "bad effects" were reported for hydromorphone. Hydromorphone also produced dose-dependent increases in the agonist scale of the adjective checklist, but no increases in the antagonist scale. On the ARCI only the MBG (euphoria) scale was increased. Naloxone produced dose-dependent increases on the visual analog scales for "drug effects", and "bad effects" (Figure 2); there were no increases in "high", "good effects", or "liking" following naloxone administration. Naloxone produced dose-dependent increases in the antagonist scale of the adjective checklist, but no increases in the agonist scale. There were no consistent naloxone effects on any scales of the ARCI.

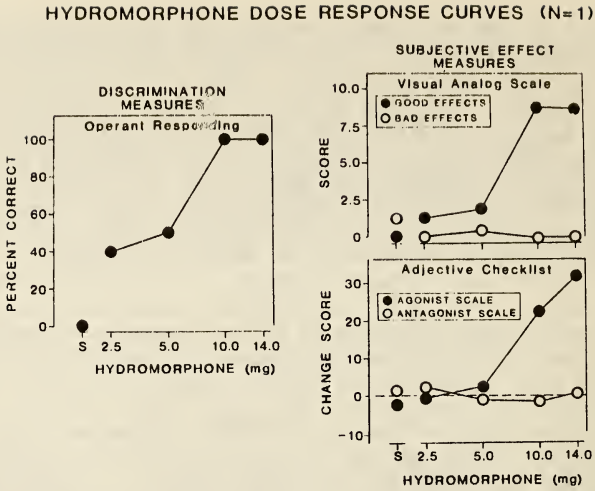


FIGURE 1. Hydromorphone Dose Response Curves (N = 1) for percent identifications as hydromorphone in operant responding discrimination measure, visual analog scale scores, and adjective checklist scale scores. Data from test drug discrimination trials (13-40), average of 2 determinations.

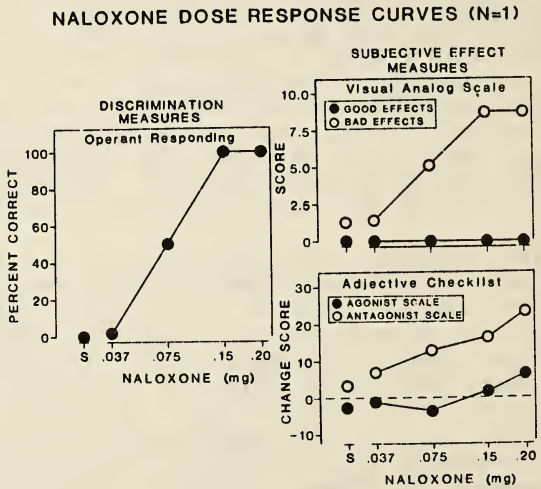


FIGURE 2. Naloxone Dose Response Curves (N = 1) for percent identifications as naloxone in operant responding discrimination measure, visual analog scale scores, and adjective checklist scale scores. Data from test drug discrimination trials (13-40), average of 2 determinations.

DISCUSSION

The results of this pilot study show that it is possible to adapt for human laboratory use the same general procedures of drug discrimination training which have been used so successfully and productively in the animal laboratory. The three-way opioid discriminations of agonist versus antagonist versus saline were rapidly learned by the methadone-dependent volunteer subjects, and orderly dose-effect relationships were observed in this human opioid drug discrimination testing. A number of different measures of drug discrimination appear to be effective, including a "percent of drug lever" operant response measure, which is commonly used in animal studies.

This behavioral drug discrimination testing was readily integrated with collection of traditional clinical pharmacology measures of subjective drug effects, and these data, too, showed orderly and comparable dose-effect relationships. This drug discrimination paradigm is not meant to replace traditional measures of subjective drug effects, but to serve as an additional source of information, which might prove to be more sensitive to low doses of drugs and which might allow better comparison between drugs within a single pharmacological class which have considerable overlap in subjective effects, such as might be expected with the mixed opioid agonist/antagonist analgesics. In addition, use of this paradigm in combination with measures of subjective drug effects will allow interesting comparisons of human and animal drug discrimination studies and the relationship between drug discrimination and verbal descriptions of drug effects. Overall, this drug discrimination paradigm appears to be a useful experimental procedure for studying the similarities and differences among the wide variety of available opioid compounds.

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Maternal Drug Use and the Effectiveness of Pharmacotherapy for Neonatal Abstinence

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Infants undergoing neonatal abstinence due to maternal drug use have been commonly treated with paregoric, phenobarbital or diazepam. This study was designed to test the effectiveness of each of these agents in the control of abstinence symptomatology. The relationship of the type of maternal drug use to the effectiveness of the treatment was also examined. The subjects included 134 infants born at Thomas Jefferson University Hospital who were treated for abstinence after careful assessment with a scoring system. Infants with serious medical complications were finally eliminated from the study. A series of least squares linear regression analyses was performed using the treatment drug, type of maternal drug (opiates, non-opiates, or both), and the interaction of treatment and maternal drugs as predictors of whether or not a second pharmacotherapeutic agent was needed in order to control abstinence symptomatology. Treatment was considered effective if control was obtained by the use of a single agent. Results revealed that if maternal drug use was limited to non-opiates, phenobarbital therapy was a significant predictor of successful treatment. Treating an infant with diazepam, however, significantly predicted the need for a second agent, regardless of maternal drug use. Paregoric was a significant predictor of successful treatment if maternal drug included opiates or a combination of opiates and other drugs. However, paregoric was also a significant predictor of unsuccessful treatment if the mother abused only non-opiates. Conclusions of the data are as follows: 1) an abstinence scoring system is essential in the assessment of any infant undergoing abstinence, 2) evaluation of the drugs used prenatally will permit more specific drug choices for treating neonatal abstinence, 3) combining a scoring system with specific drug recommendations provides a more objective method of management, 4) paregoric is most efficacious if the infant has prenatal exposure to opiates or a combination of opiates and other agents, 5) phenobarbital is most efficacious if the infant is prenatally exposed to non-opiates only and finally, 6) diazepam is not an appropriate drug for neonatal abstinence either from prenatal exposure to opiates only, opiates and non-opiates or non-opiates only.

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Double-Blind Comparison of Desipramine and Placebo in Withdrawal From Cocaine Dependence

Forrest S. Tennant, Jr., and Anita L. Tarver

ABSTRACT

Desipramine was compared with a placebo under double-blind conditions to determine if it is effective treatment for withdrawal from cocaine dependence. Eleven (11) subjects received desipramine and 11 received placebo. There was no significant statistical difference between groups in self-report on effectiveness; retention in treatment; cessation of cocaine use; or suppression of withdrawal scores. Although desipramine appears to be no more effective than placebo in withdrawal from cocaine use or suppression of withdrawal scores, it may be useful in the long-term treatment of this condition.

INTRODUCTION

Desipramine has recently been suggested as a possible treatment for cocaine dependence.[1,2] This tricyclic antidepressant produces as great or greater degree of selective blockage of norepinephrine re-uptake as any other antidepressant.[3] Chronic cocaine administration to animals and *in vivo* has been shown to deplete neuronal norepinephrine levels.[4] Based on this information, it was believed that desipramine may be an effective treatment agent for chronic cocaine dependence, and an open clinical trial plus anecedotal reports have indicated this may be an effective treatment.[1,2] Reported here is a double-blind, placebo-controlled clinical trial to determine if desipramine may be effective in withdrawal from cocaine dependence.

METHODS

Twenty-two (22) cocaine-dependent subjects were admitted to a

special cocaine research unit located in Eastern Los Angeles County (West Covina). In order to be admitted to the study, the subject had to have a perception that cocaine dependence existed to the point that medical withdrawal was necessary. All subjects also had to meet the following criteria: multiple daily cocaine use for the previous one month; no other drug or alcohol dependency; absence of any illness requiring medication; and presence of cocaine in plasma or urine.[3] One-half (11) of subjects were randomly assigned to desipramine and one-half (11) to placebo groups. Subjects attended the clinic daily for the first five days and then two times per week for as long as five additional weeks for a maximal study time of six weeks (42 days.) Desipramine and placebo were prepared in identical unmarked capsules. Each active capsule contained 25 mg. of desipramine. Neither subject nor clinical staff were aware of contents of capsules. The first day's dose was one capsule given four separate times so that a subject receiving active medication would consume 100 mg in 24 hours. Daily dosage was raised to a maximum of six capsules or 150 mg of desipramine in 24 hours if the subject complained that medication was ineffective.

On each day of attendance subjects were asked if the medication "worked," reduced cocaine craving, gave energy, prevented depression, and assisted sleep. One nurse observer determined a withdrawal score for each of the first five days of the study by assigning a numerical score to 14 symptoms: 0 for absent; +1 for mild; +2 for moderate; and +3 for severe. The following symptoms were assessed: anorexia; diaphoresis; insomnia; irritable; anxiety; lethargy; nausea; diarrhea; depression; headache; difficulty concentrating; cocaine craving; myalgia; and mental confusion. A urine specimen was taken every other day of attendance during the first week and every day of attendance after the first week. The qualitative presence of cocaine in each urine sample was determined by immunoassay technique.[5]

If a subject felt their assigned medication was ineffective, they could drop out of the study or be given doses of desipramine.

RESULTS

Study groups appeared comparable with the exception that all females received desipramine. (Table One) All subjects were chronic cocaine users who believed themselves to be dependent and in need of medical withdrawal treatment. Self-report effectiveness for reduction of craving, providing energy, preventing depression, and assisting sleep showed no difference between the two groups with the exception that the placebo group reported more assistance with sleep. (Table Two) Drop-out rate, mean days retained in treatment, and number of subjects who converted urine from cocaine positive to negative, and total number of cocaine negative urine tests were not statistically different. (Table Two) In addition, the mean daily withdrawal score for each group during the first five days was not statistically different for any day, and the overall mean daily withdrawal score for the first five days was almost identical (6.0 versus 5.9). All appeared to clinically benefit from it and they voluntarily continued it for periods ranging from one to six months. The only side effect reported by either group was dry mouth in two desipramine subjects.

DISCUSSION

Although all females were assigned in blind, random fashion to the desipramine group, it is highly improbable that statistical outcome has been affected. Even if some poor-performing females had been assigned to the desipramine group, performance data betw en comparison groups is so similar that enough variance with different group assignments could probably not be achieved to affect statistical outcomes. Clinical performance of placebo and desipramine groups appeared to be essentially identical by subject self-report, drop-out rate, retention, withdrawal suppression, and cocaine use as detected by urine test. The only difference between groups appeared to be that more subjects in the placebo group reported ability to sleep. No significant side-effects were reported to occur in the desipramine group even though it was administered, in some cases, within only a few hours following cocaine usage.

Desipramine is a potent re-uptake blocker of norepinephrine.[3] Cocaine appears to deplete neurons of norepinephrine.[4,6] Prior to this study, we had hoped that desipramine's ability to block the re-uptake of norepinephrine would make more norepinephrine available to receptor sites and facilitate withdrawal from cocaine dependence. It may be that cocaine depletes central nervous system norepinephrine so much that desipramine cannot be effective in the acute phase of withdrawal from cocaine dependence. Marked norepinephrine depletion has been demonstrated in animals that were administered cocaine on a chronic basis.[4] In addition, another recent, unreported study by us suggests that norepinephrine is markedly depleted in cocaine-dependent persons, since urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) was very low in study subjects. Imipramine, which partially converts to N-desmethyl-imipramine, the active metabolite of desipramine, has been shown to lower MHPG excretion.[7] It is, therefore, possible that further lowering of norepinephrine by desipramine could be the explanation for the placebo group reporting more ability to sleep. Demonstration that desipramine is no more effective than placebo in the acute withdrawal from cocaine dependence raises questions about the usefulness of all tricyclic antidepressants for this condition. We observed, however, that desipramine appeared to be clinically helpful to some subjects after the acute withdrawal phase of cocaine dependence had ended.

TABLE ONE
DEMOGRAPHIC AND DRUG USE
CHARACTERISTICS OF STUDY GROUP

	Desipramine N=11	Placebo N=11	Stat Sig
Males	7 (63.6%)	11 (100%)	P < .05
Females	5 (45.4%)	0 (0%0	P < .05
Age Range (Years)	18 - 35	19 - 36	NA
Mean Age (Years)	28.0	29.3	PNS

TABLE ONE
(Continued)

	Desipramine	Placebo	Stat Sig
Employed	7 (63.6%)	6 (54.5%)	PNS
Married	4 (36.4%)	4 (36.4%)	PNS
Range Overall Cocaine Use (Years)	1 - 14 yrs.	2 - 10 yrs.	NA
Mean Overall Use of Cocaine (Months)	49.4	66.2	PNS
Mean Reported Amount Used per day (gms)	1.32	1.54	PNS

TABLE TWO
RESULTS AND OUTCOMES OF TREATMENT

	Desipramine N=11	Placebo N=11	Stat Sig
Feels Medication Does Following:			
"Works"	6 (54.5%)	7 (63.6%)	PNS
Reduces Cocaine Craving	7 (63.6%)	7 (63.6%)	PNS
Gives Energy	0 (0%)	3 (27.3%)	PNS
Prevents Depression	6 (54.5%)	5 (45.5%)	PNS
Assists Sleep	3 (27.3%)	5 (45.5%)	$P < .05$
Dropped out in First Week	5 (45.5%)	5 (45.5%)	PNS
Mean Days in Treatment	12.0	14.8	PNS
Urine Tests Absent of Cocaine	39 of 61 (63.9%)	47 of 67 (70.1%)	PNS
No. Who Converted Urine from Cocaine Positive to Negative	9 (81.8%)	8 (72.7%)	PNS
Switched to Known Desipramine Following Drop-Out from Study	3 (27.3%)	5 (45.5%)	PNS
Mean Per Day Withdrawal Score During First Five Days of Treatment	6.0	5.9	PNS

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Platelet Serotonin Transporter in Cocaine Patients

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INTRODUCTION

Cocaine is a potent euphoriant which has become a growing medical and social problem. While the euphoriant properties of this drug are well known, there is less appreciation of cocaine-associated depressive states. Depressive syndromes occurring after the abrupt discontinuation of cocaine are particularly frequent and may lead to self-medication with cocaine and the perpetuation of cocaine abuse. While it is not clear in all cases whether depressive symptoms preceded or resulted from cocaine abuse, such syndromes may require specific treatment. At present there are no laboratory measures with proven reliability that are specific for depression in cocaine patients. A reliable test for depression in cocaine abusers might be useful in order to distinguish between pre-existing depression and cocaine-induced affective changes. One recently reported laboratory measure for major depression is the platelet serotonin transporter (PST). Since cocaine itself could affect this measure, however, the specificity of the PST must be tested in cocaine abusers who are not depressed. This study addresses PST findings in nondepressed cocaine patients.

The PST measure relates to the indolamine theory of depression which states that depression can result from a deficiency of serotonin in the neuronal synapse. Numerous measures of serotonin metabolism have previously been shown to be abnormal in certain patients with major depressive illness. These include cerebral spinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA), and plasma and CSF tryptophan levels (Ashcroft and Sharman 1960; Van Praag and Korf 1971; Goodwin et al. 1977; Bridges et al. 1976; d'Elia et al. 1979). The most recent serotonin measure, the PST, involves the uptake of serotonin by platelets and serves as a peripheral model for serotonin uptake in brain serotonin nerve endings (Sneddon 1973; Stahl and Meltzer 1978; Pletscher 1968). This measure has been suggested to have diagnostic reliability for depression based upon low PST values in endogenously depressed patients (Meltzer et al.

1981). Decreased platelet serotonin uptake in depressed patients was found by Meltzer and his colleagues (Meltzer et al. 1981; Meltzer et al. 1983). Malmgren found similar results when comparing endogenously depresssed patients with those who were nonendogenously depressed and with normal controls (Malmgren et al. 1981). Kaplan and Mann (1982) have also found platelet uptake of serotonin in depressives to be significantly lower than in controls. However, the specificity for depression of the PST has not been addressed in patients with other conditions, such as cocaine abuse.

Cocaine has been reported to alter serotonin and other neurotransmitter metabolism in a number of ways (Dackis and Gold 1984). In animal studies, cocaine reduces brain serotonin concentrations acutely (Pradhan et al. 1978a) and this reduction may contribute to behavioral effects of the drug (Pradhan et al. 1978b). Cocaine also inhibits the synthesis of serotonin (Knapp and Mandell 1972; Schubert et al. 1970) leading to a reduction in serotonin turnover. Reduced serotonin turnover has been hypothesized to result from increased stimulation of postsynaptic serotonin receptors (Friedman et al. 1975), representing a compensatory regulatory mechanism. Cocaine also blocks serotonin reuptake (Friedman et al. 1975; Ross and Renyi 1969), leading to increased synaptic levels of serotonin. Whether this potentiation of serotonin neurotransmission leads to compensatory turnover reductions remains unclear.

It is obvious from animal studies that cocaine exerts a number of significant effects on serotonin function in the brain. It is quite possible that serotonin systems are likewise disrupted in human cocaine abusers. For this reason, as well as previously discussed considerations regarding the diagnostic reliability for depression of the PST, we decided to investigate this measure in cocaine patients. Our hypothesis was that, as in animal studies, serotonin reuptake would be inhibited in humans chronically exposed to cocaine, and that this would be reflected in low PST values.

METHODS

Subjects: Subjects consisted of 24 cocaine patients and 28 normal controls. All subjects were free from a present or past DSM-III diagnosis of major depression as determined by a careful psychiatric interview. Cocaine patients had a current DSM-III diagnosis of cocaine abuse and were free of other substance dependence. The DSM-III diagnosis of cocaine abuse was confirmed in all cases by either blood or urine levels of cocaine on admission. PST assays were performed within 5 days of admission on cocaine patients.

PST Assay: Specimens for the determination of PST were collected in BD yellow top vacutainers containing ACD (Acid

Citrate Dextrose) as an anticoagulant. The tubes were spun at 200 x g for 10 minutes in a refrigerated centrifuge set at 4-10°C. Once spun, the platelet rich plasma was carefully removed with a polypropylene transfer pipet and placed into a conical 10 ml polypropylene tube. Adequate buffer was added to double the volume of the harvested platelet rich plasma and the resulting concentrations of platelets were determined in triplicate by a Baker MK-4/HC electronic platelet counter. The method of determining PST is a modification of a method previously described (Arora and Meltzer 1981). Radioactive serotonin was diluted with buffer to achieve final concentrations varying from 3.75×10^{-5}M to 1.00×10^{-6}M. The diluted platelet rich plasma was preincubated for 10 minutes at 37°C and then 300 uL aliqots were combined with 600 uL of buffer and 100 uL of varying concentrations of radiolabelled serotonin. These tubes were incubated for 2 minutes at 37°C then immediately placed in an ice bath to stop the reaction. Tubes were centrifuged at 0-4°C at 14000 g in a microfuge (Fisher Model 235A), the supernatant discarded and the platelet pellets washed with 700 uL of buffer to remove any radiolabelled serotonin not transported by the platelets. The pellets were then solubilized in 500 uL of ScintiGest (Fisher Scientific) at 50°C for 2 hours. Once solubilized, the platelet pellet was transferred to a scintillation vial containing 7.0 mls of SintiVerse II (Fisher Scientific) and counted in a Beckman LS 7500 liquid scintillation system. Uptake for each concentration of radiolabelled serotonin transported into aliquots of platelet rich plasma was then determined as maximum velocity. Values obtained by using Lineweaver Burk Analysis (Lineweaver and Burk 1934) data was expressed as "serotonin units" defined as molecules of serotonin transported per platelet (5-HT/platelet x 10^5). Inter- and intra-run coefficients of variation (C.V.) for split control samples were less than 10.0 percent. All above operations, including the preparation of the platelet rich plasma, were carried out in the shortest time possible to avoid loss of activity.

RESULTS

PST values of the cocaine and normal control groups were compared by means of a two-tailed student's t-test. PST values in cocaine patients (16.3 $\pm$ 5.7, mean $\pm$ SD) were lower than those of normal controls (27.2 $\pm$ 11.0, mean $\pm$ SD). This difference was statistically significant ($t=4.86$, $df=50$, $p < 0.001$).

DISCUSSION

Our data indicate that the PST is extremely low and therefore not specific for depression in cocaine abusers. Although none of the cocaine abusers were clinically depressed, their PST values were extraordinarily lower than seen in our control

subjects. Low PST values in patients suspected of cocaine abuse may even indicate the need for plasma or urine testing for cocaine and a careful drug history. The clinician should cautiously interpret PST results in cocaine users, and perhaps in other untested conditions. The current findings suggest the need for further research regarding the specificity of the PST measure and militate against its diagnostic use for depression in cocaine patients.

If the PST serves as an accurate model of central serotonin neuronal reuptake, our low PST values in cocaine users would imply a potentiation of central serotonin neurotransmission in these patients. This finding would be consistent with reports that cocaine blocks reuptake in animals (Friedman et al. 1975; Ross and Renyi 1969). Cocaine-induced neurotransmitter disruptions, such as reuptake blockade, could persist well beyond the last cocaine dose and exert pressure on brain homeostasis. As such, this disruption could contribute to abstinence symptoms in areas influenced by serotonin functions, such as sleep, locomotor activity, mood, appetite regulation, and aggression (Kizer and Youngblood 1978; Fuller 1982).

We anecdotally observed several predictable symptoms after abrupt cocaine discontinuation which may represent a withdrawal syndrome. These symptoms included depression, anergia, irritability, and craving for cocaine. Neurochemical effects of cocaine, such as changes in serotonin reuptake, could be related to "psychological" tolerance and withdrawal commonly encountered in cocaine abuse. Further research is required to determine whether PST abnormalities in cocaine users are pre-existing or result from cocaine abuse. A longitudinal study of PST in recently abstinent cocaine users could clarify this question.

Our recently abstinent cocaine abusers and certain depressed patients appear to share low PST values. It is possible that mood changes seen during and after cocaine use vary with serotonin uptake measures. This possibility is interesting in light of the fact that several antidepressant medications block serotonin uptake and that this blockade has been theorized as the mechanism of antidepressant action. Depressed patients abusing cocaine may differ from nondepressed cocaine abusers with respect ot the PST. PST inhibition may also recover in accordance with depressive symptoms seen after cocaine is discontinued. These speculations require further investigation.

In conclusion, our findings indicate that, as a marker of major depression, the PST probably lacks adequate specificity in cocaine abusers. This test must be carefully interpreted when used diagnostically for depression in cocaine addicts because cocaine abuse itself profoundly influences the PST measure. Low PST values in cocaine abusers suggest an additional pharmacological effect of cocaine which could further our

understanding of cocaine abuse and the mechanism of cocaine induced mood alterations.

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Impact of Talwin NX

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INTRODUCTION

During the decade of the seventies, remarkable changes occurred in the heroin scene in the Chicago area. White heroin, with a distribution network centered in the black ghetto, was replaced with brown heroin, with the distribution network now shifted to the Hispanic community. In addition to the change in control of the distribution network, increased efforts by law enforcement agencies appeared to cause longer periods of unavailability of quality heroin.

It is tempting to speculate that the longer periods of unavailability of quality heroin created a vacuum into which "T's and Blues" flowed. During this decade Chicago area treatment programs experienced such a dramatic rise in the intravenous use of pentazocine and tripelennamine, known as "T's and Blues", that by the end of this time, almost one half of the heroin addicts in treatment were frequent users of "T's and Blues". In addition, ten percent of the addicts in Chicago area treatment programs at this time were considered to be primary "T's and Blues" abusers, many of whom did not use heroin frequently and some had never used heroin at all.

By 1978, pentazocine ranked fifth among drugs coming to attention in Chicago area emergency rooms. Illinois reacted to this dramatic increase in abuse by scheduling pentazocine as a schedule two drug in 1979. Sterling-Winthrop reacted by formulating Talwin Nx, a combination of pentazocine, 50 mg. and naloxone, 0.5 mg.

The work we describe in this paper was undertaken in the Spring of 1983 to study the effects of the introduction of Talwin Nx. At this time, according to reports from Chicago area treatment providers, demand for treatment of the primary pattern of "T's and Blues" was diminishing; none the less, clinical encounters with primary abusers of the combination occurred, and "T's and Blues" were a familiar and apparently enduring part of the drug scene in Chicago.

METHOD

We conducted this study at the University of Chicago Drug Abuse Rehabilitation Program. Groups of subjects were interviewed in the following periods:

Phase 1 May 20th to June 7th, 1983 (N = 34)
Phase 2 - June 15th to July 14th, 1983 (N = 92)
Phase 3 - August 24th to August 26th, 1983 (N = 24)

When the data from these periods was examined it was decided that additional data would be obtained. Interviews were then conducted in the second part of the study in the following periods:

Phase 1 - October 6th to October 17th, 1983 (N = 50)
Phase 2 - November 14th to November 18th, 1983 (N = 40)
Phase 3 - December 5th to December 9th, 1983 (N = 60)

The research subjects were recruited for this study by the University of Chicago Drug Treatment Clinic's clients and staff. Each subject was assigned a number to assure complete anonymity; also no identifying information was obtained from the subjects which could associate them with the study in the future. One researcher conducted all the interviews and did not interview the same subject twice.

All subjects were administered identical questionnaires in a standardized format.* Questions concerning heroin use were included in the questionnaire to make it appear that our focus of interest was on multiple drug use patterns rather than exclusively on "T's and Blues". In this way we hoped to avoid bias.

Each subject was paid $10.00 per interview. Interviewing lasted approximately fifteen minutes per subject. Subjects were also required to submit urine samples which were tested for the presence or absence of pentazocine. Subjects were informed at the beginning of their interviews that their street drug patterns were to be studied.

In the second part of the study we incorporated additional measures to further validate our findings. In the initial stages of part 2, difficulty was experienced in obtaining subjects who were willing to bring in a Talwin tablet to the clinic. We therefore instituted a "finder's fee". This fee consisted of paying "finders"; for example, clients of the clinic or subjects who had already been interviewed, $5.00 for each subject they secured for the study. In this part of the study we also selected urine samples on a random basis for comprehensive analysis. We also required each subject to present a Talwin tablet to the researcher in order to gain entrance into the study. We added this measure to ensure that subjects had at least a peripheral relationship with the illegal distribution system. None of the subjects claimed to be using Talwin on a prescribed basis for a medical condition in either part of this study.

* A copy of the questionnaire can be obtained from the authors by written request.

RESULTS

The results of this research are reported in the tables below. Table 1 depicts the results of the questionnaire from the three phases of the study.

TABLE 1

Questionnaire Data (Part 1)

	Phase 1	Phase 2	Phase 3
	May 20 to June 7	June 15 to July 14	August 24 to August 26
	N=34	N=92	N=24
$\bar{X}$ age of respondents	32	28	40
Race: Black	86%	100%	100%
White	14%	-	-
Sex: Male	65%	79%	88%
Female	35%	2%	13%
1) $\bar{X}$ age of first use of "T's & B's"	27	29	33
$\bar{X}$ age of first use of heroin	21	20	19
2) $\bar{X}$ number of years in life using "T's & B's" 2 months or more during the year and at least 3 x a week during use	6 (N=30)	5 (N=90)	7 (N=23)
3) $\bar{X}$ number of uses per subject of "T's & B's" last month (30 day month)	57 (N=31)	36	49
$\bar{X}$ number of uses per subject per day	2	1	2
4) $\bar{X}$ number of uses per subject of heroin last month (30 day month)	20 (N=24)	15 (N=73)	15 (N=22)
$\bar{X}$ number of uses per subject per day	.6	.5	.5
5) Quality of "T's & B's" (% of responses):			
Would not touch it (bad news)	9%	15%	4%
Worse than ever	38%	49%	67%
Same as ever	32%	30%	25%
Better than ever	12%	5%	4%
Best it's ever been	9%	1%	0%

TABLE 1 (continued)

(5 continued)			
% of subjects reporting various forms of Talwin use:			
Yellow - (Talwin Nx)	11%	14%	26%
Peach (Talwin 50)	70%	74%	71%
Blue (Talacen)	14%	9%	3%
Other (Talwin compound)	5%	3%	0%
6) Quality of heroin, % of responses:			
Would not touch it (bad news)	0%	14%	14%
Worse than ever	24%	31%	45%
Same as ever	40%	16%	14%
Better than ever	24%	36%	27%
Best its ever been	12%	3%	0%
% of positive Talwin Screens	29%	8%	0%

Table 2 depicts the data analyses for the three phases of Part 2 of the research.

TABLE 2

Questionnaire Data (Part 2)

	Phase 1	Phase 2	Phase 3
	October 6 to October 17	November 14 to November 18	December 5 to December 9
	N=50	N=40	N=60
$\bar{X}$ age of subjects	33	35	33
Race: Black	100%	100%	100%
Caucasian	0%	0%	0%
Sex: Male	76%	70%	78%
Female	24%	30%	22%
1) $\bar{X}$ age of first use of "T's & B's"	27	28	27
$\bar{X}$ age of first use of heroin	20	21	21
2) $\bar{X}$ number of years in life using "T's & B's" 2 months or more during the year and at least 3 x a week during use	6	5	5

TABLE 2 (continued)

3) $\bar{X}$ number of uses per subject of "T's & B's" in the previous month (30 day month)	60	35	42
$\bar{X}$ number of uses per subject per day	2	1.2	1.4
4) $\bar{X}$ number of uses of heroin per subject in the previous month (30 day month)	41 (N=41)	37 (N=37)	23 (N=56)
$\bar{X}$ number of uses per subject per day	1.4	1.2	.8
5) Quality of Talwin, % of responses:			
Would not touch it (bad news)	4	3	2
Worse than ever	46	65	58
Same as ever	48	27	35
Better than ever	2	5	5
Best it's ever been	0	0	0
% of subjects reporting various forms of Talwin use:			
Yellow (Talwin Nx)	90%	87.5%	93%
Peach (Talwin 50)	62%	45%	27%
Blue (Talacen)	-	-	-
Other (Talwin Compound)		2.5% (White)	
6) Quality of heroin, % of responses:			
Would not touch it (bad news)	0	3	2
Worse than ever	29	38	52
Same as ever	34	46	37
Better than ever	34	13	9
Best its ever been	3	0	0
% of positive Talwin Screens	10%	3%	2% (59 urines)
% of positive Talwin pill analyses	100%	100%	100%

The majority of the subjects interviewed were black males with a mean age of 33 years. "T's and Blues" use began approximately at 29 years of age for these subjects and continued at a rate of approximately three times a week or more for at least two months each year for approximately six years. The age of their first use of heroin was approximately 20 years. This figure was consistent across all six phases of the research.

Table 3, in which we combined categories from Table 1 and 2 to

highlight changes, illustrates the subjects' changing perception of "T's and Blues" and heroin as the study progressed.

TABLE 3

Comparison of Qualities of Talwin and Heroin

		Bad news worse than ever	Same as ever	Better than ever best its ever been
Quality of Talwin		%	%	%
Part 1	Phase 1	47	32	21
	Phase 2	64	30	5
	Phase 3	71	25	4
Part 2	Phase 1	50	48	2
	Phase 2	68	27	5
	Phase 3	60	35	5
Quality of Heroin				
Part 1	Phase 1	24	40	36
	Phase 2	45	16	39
	Phase 3	59	14	27
Part 2	Phase 1	29	34	37
	Phase 2	41	46	13
	Phase 3	54	37	9

By the conclusion of Part 1 of the study over 70% of the subjects perceived "T's and Blues" to be "worse than ever" or "bad news". This level of dissatisfaction with "T's and Blues" continued throughout the second part of this study.

According to the reports of the subjects, particularly in the later periods of the study, "T's and Blues" were no longer used as primary intoxicants. They were then primarily used as "boosters" for poor quality heroin. Since the perceived quality of heroin decreased in the latter part of the study, many of the subjects felt that they needed to increase the number of sets of "T's and Blues" injected along with heroin in order to obtain intoxication.

The increase in the use of Talwin Nx from May to December may have been partially due to the scarcity of peach colored Talwin and its high cost, $12 to $20 a set for a T-21 (original Talwin without Nx) and blue, relative to $7 a set for a Talwin Nx and a blue.

Many of the subjects stated that Talwin Nx, known to them as "footballs", "bananas", or "butterballs" were not as potent as T-21's. One subject described the effects of Talwin Nx as follows:

"With the originals (peach colored T-21), I used to get a good nod and be able to wake up in the morning and feel cool, now with Talwin Nx I feel jittery when I wake and I have to go out and look for dope, i.e. heroin."

Following use of "T's and Blues", subjects also reported a high incidence of dysphoric side effects including nausea, paranoia, diarrhea, abscesses, darkening and burning of the skin, increased agitation, and seizures. In some instances, seizure activity was a concomitant to the increased dosage levels of "T's and Blues". Several of the subjects interviewed in this study used more than four sets of "T's and Blues" on an individual basis per injection. The majority of subjects, however, hesitated in using such a large number of sets for fear of unpleasant effects.

It is important to add that the compounds present in the urines analyzed via comprehensive urine screens indicated the subjects used a variety of drugs. Of the thirty urines analyzed via comprehensive urine screens in the second part of the study, urine specimens were positive for the following compounds:

#01 - acetaminophen; cannabinoids
#05 - cannabinoids; unident material (unidentified)
#10 - ethanol
#15 - acetaminophen; ethanol
#20 - quinine; ethanol
#25 - norpropoxyphene; ethanol; cannabinoids
#30 - quinine; ethanol; cannabinoids
#35 - quinine; ethanol; cannabinoids
#40 - pentazocine; tripelennamine; quinine; ethanol
#45 - quinine; ethanol; cannabinoids
#50 - ethanol
#55 - codeine; methadone; cannabinoids
#60 - salicylates; acetaminophen; codeine; quinine; cannabinoids; benzodiazepine metabolites
#65 - ethanol; cannabinoids
#70 - codeine; chlordiazepoxide; cocaine; benzoylecgonine; quinine
#75 - ethanol
#80 - methadone; cocaine; benzoylecgonine; cannabinoids
#85 - acetaminophen; ethanol
#90 - ethanol; cannabinoids
#95 - clean
#105 - insufficient urine; not tested
#115 - ethanol; cannabinoids
#120 - codeine; propoxyphene; ethanol
#125 - ethanol
#130 - benzodiazepine metabolites
#135 - phencyclidine; cannabinoids
#140 - clean
#145 - cannabinoids
#150 - ethanol; tripelennamine; antihistamine; valium

One hundred fifty Talwin Nx tablets were purchased in Part 2 of the study. Of the 150 tablets, 30 were analyzed to test for the presence or absence of pentazocine, and 100% of these analyses were positive for pentazocine.

DISCUSSION

The data obtained in this study suggests that the inclusion of a small dose of naloxone substantially alters the street patterns of abuse of the Talwin and Pyribenzamine combination. The demand for treatment for primary abuse of this combination declined dramatically following the introduction of Talwin Nx in the Spring of 1983. There were also marked changes in the experiences obtained from the use of T's and Blues and in the frequency with which this combination was used as a primary source of intoxication.

Studies of this nature are difficult because of the multiple drug use patterns of so-called "street people". Our broad screen urines revealed substantial evidence of such drug use in the cohort studied. In addition, changes in the supply and potency of heroin affected users' drug selections.

The situation is also made difficult by the fact that many users of "T's and Blues" and heroin have minimal or nonexistent degrees of pharmacologic dependence on opioids. This alters substantially the response to intravenous naloxone. If there is no opioid dependence, then the experience of taking Talwin Nx will be quite different than if opioid dependence is present.

Reports from treatment programs in the Chicago area indicate that demand for treatment of the primary abuse of T's and Blues is practically nonexistent at this point. For example, the perinatal program which focused on pregnant T's and Blues users, at the Chemical Dependence Unit at Northwestern University had to be terminated because no pregnant addicts are being encountered now who are primary users of "T's and Blues". Reports from treatment providers across the Chicago area are quite consistent in this regard.

There is evidence from both formal and informal channels that the introduction of Talwin Nx appears to have the effects hoped for when it was introduced; namely, reduction in primary abuse of Talwin and Pyribenzamine. Further studies are needed to document the persistence or perhaps reversal of this trend.

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Contingent Methadone Dose Increases as a Method for Reducing Illicit Opiate Use in Detoxification Patients

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Outpatient methadone detoxification is a common treatment for opiate dependence, but is often found to be ineffective in achieving even short-term abstinence. Typically, patients drop out of treatment or relapse to the use of illicit opiates prior to completion of the detox (Canada, 1972; Stitzer et al., 1981; Wilson et al., 1974). Stitzer et al. (1981), for example, reported that 80% of their patients relapsed to illicit-opiate use prior to or shortly after the completion of a 90-day detox. Such high rates of relapse have been reported both for individuals who periodically used illicit opiates throughout the detox as well as those who were initially abstinent (Stitzer et al., 1983a). In general, then, outpatient methadone detoxification is typically ineffective, and methods for increasing its clinical efficacy should be identified if the use of this treatment modality is to continue.

One method for increasing abstinence from illicit opiates and also achieving greater retention in treatment has been to include contingency-management procedures in the detox (Hall et al., 1979; McCaul et al., 1984). For example, McCaul et al. (1984) provided patients enrolled in a 90-day detox with $10.00 and a take-home dose contingent on each opiate-free urine sample delivered during twice weekly testing. The contingency achieved (1) an increase in the overall percentage of opiate-free urines, (2) an increase in the maximum number of consecutive opiate-free urines individuals provided, and (3) an increase in treatment retention. The purpose of the present study was to further investigate the use of contingency-management procedures with individuals enrolled in outpatient methadone detoxification. More specifically, in this study we investigated the effectiveness of contingent methadone-dose increases in reducing illicit-opiate use and increasing treatment retention. Contingent methadone-dose increases have been used to reduce illicit-opiate use in methadone maintenance patients (Stitzer et al., 1983b) and could prove to be a more economically feasible procedure than providing money for opiate-free urines during outpatient methadone detoxification.

METHOD

Patients. Thirty-five male patients dependent on illicit opiates were enrolled in a 90-day or 13-week detoxification program across an 11-month period. Patients had to provide 50% or more opiate-free urines during the first 3 weeks of the detox to be eligible for the present study. Twenty-seven of the 35 patients met this criterion and the remaining eight patients were assigned to another study.

Procedures

Attendance and urinalysis. Patients reported to the clinic 7 days a week and were terminated from treatment when they missed any 3 consecutive days at the clinic. Urine samples were collected on Monday, Wednesday, and Friday and were immediately tested via an onsite Emit system for the presence of opiate drugs. Additionally, one randomly selected sample each week was sent out to an independent laboratory for each patient throughout the detox. These samples were tested using thin layer chromatography (TLC) analysis for both opiate and nonopiate drugs. All specimens were collected under staff observation to prevent patients from providing bogus urines. Missed urine specimens due to clinic absences were counted as opiate positives.

Contingency-management procedure. Patients were randomly assigned to one of three treatment groups, which became effective on Day 22, the first day of Week 4. The three treatment groups were a contingent methadone-dose increase group, a noncontingent methadone-dose increase group, and a control group. The procedural differences between the groups were as follows: 1) Members of the contingent group (N = 9) could increase their clinic dose of methadone by 5, 10, 15, or 20 mg on a daily basis, but only if their most recent urine sample was free of opioids other than methadone. 2) Members of the noncontingent group (N = 8) had the same amount of extra methadone available to them as the contingent group, but could receive daily dose increases independent of their urinalysis results. 3) Members of the control group (N = 10) could not receive dose increases. Dose increases were always voluntary and they were available from Day 22 (Week 4) through Day 77 (Week 11) of the 90-day detox.

Methadone-dosing regimen. Patients drank their methadone daily under nursing supervision. Methadone doses were mixed with cherry syrup and administered under double-blind conditions. Dose increases were added to the clinic dose by the nurse upon request. During the first 3 weeks of the detox, all patients were stabilized on 30 mg of methadone. Beginning in Week 4 the methadone dose was reduced in alternating 2 and 3 mg steps until 0 mg was reached at the end of Week 9. Thereafter, control subjects received only cherry syrup as their clinic dose. Members of the contingent and noncontingent groups also received cherry syrup as their clinic dose during Weeks 10 and 11, but still had the dose increases available to them during this period. When the dose increases were discontinued on Day 78, the clinic dose for the contingent and noncontingent group members was increased to 15 mg and reduced again to 0 mg in 5 mg decrements every 3 days. This was done to prevent an increase in withdrawal symptoms after opportunities for dose increases were discontinued.

Data analysis. Data for the three groups are presented for treatment retention, clinic attendance, and urinalysis results. All patients enrolled in the study were included in the treatment-retention analysis. However, only those patients who were retained in treatment into Week 8 of the detox (78% of the total sample) were included in the analyses of clinic attendance and urinalysis results. Early dropouts were excluded because we were especially interested in comparing the treatment groups during the later segment of the detox when the methadone dose fell below 10 mg (i.e., Weeks 8 through 11). It is during this period that high rates of relapse to illicit-opiate use often occur. Clinic attendance and urinalysis results were analyzed in two-week blocks for those who remained in treatment into Week 8. Patients discontinued from treatment during or after Week 8 were included in later analyses by assigning them their average score from the two-week block during which they terminated treatment.

RESULTS

Treatment retention. The percent of individuals in the three treatment groups discontinued during each two-week block of the dose-increase intervention procedure is presented in Table 1. In the contingent group, zero terminations occurred during Weeks 4-5, 22% or two of the original nine group members terminated treatment during Weeks 6-7, zero terminated during Weeks 8-9, and 22% or two more of the original nine terminated treatment during Weeks 10-11. In total, 44% of the contingent group members terminated treatment during the intervention period and 56% completed it. In the noncontingent group, zero terminations occurred during Weeks 4-5, 25% or two of the original eight members terminated during Weeks 6-7, and 13% or one group member terminated during Weeks 8-9 and Weeks 10-11, respectively. In total, one-half of the noncontingent group members completed the intervention. In the control group, 10% or one of the original 10 group members terminated treatment during Weeks 4-5, 10% more at Weeks 6-7, and 30% more terminated during Weeks 8-9 and 10-11, respectively. In total, 80% of the control group terminated treatment prior to completion of the intervention period. These differences across groups were not statistically significant, but the trend is clearly one of the two dose-increase groups engendering greater retention in treatment than the control group. Note that the two individuals in each group who terminated treatment prior to Weeks 8-9 are not included in the clinic-attendance and urinalysis results reported below.

TABLE 1
Percent of Subjects Terminating Treatment

	Study Weeks			
Treatment Groups	4-5	6-7	8-9	10-11
Contingent	0	22	0	22
Noncontingent	0	25	13	13
Control	10	10	30	30

Clinic attendance. Figure 1 depicts the percent of clinic absences during the dose-stabilization and intervention periods. The three groups exhibited similar levels of clinic absences during the dose-stabilization period; however, the control group exhibited a higher percent of clinic absences during the intervention period than either the noncontingent or contingent groups. A mixed two factor analysis of variance with repeated measures showed significant repeated measures ($df = 4,72$, $F = 10.68$, $p < 0.01$) and interaction ($df = 8,72$, $F = 2.24$, $p < 0.05$) effects. Post-hoc analyses using the Scheffe test indicated the control group was absent from clinic significantly more than both the contingent ($p < 0.01$) and noncontingent ($p < 0.05$) groups at Weeks 8-9 and Weeks 10-11. The differences between the noncontingent and contingent groups were not statistically significant.

Urinalysis results. Figure 2 depicts urinalysis results for the three treatment groups. During the dose-stabilization period (Weeks 2-3), all three groups were similar, presenting in the range of 12-15% opiate-positive samples. Although the control group presented a higher percentage of opiate-positives than the two dose-increase groups during Weeks 4-5 and 6-7, the three groups most clearly separated from each other during Weeks 8-11 when the clinic dose of methadone fell below 10 mg. A mixed two factor analysis of variance with repeated measures revealed significant treatment effects ($F = 3.8$, $df = 2,72$, $p < 0.05$) and significant repeated measures effects ($F = 8.5$, $df = 4,72$, $p < 0.01$). Post-hoc analyses using the Scheffe test indicated that the contingent group presented a significantly lower percent of opiate-positive urines than the control group at Weeks 8-9 ($p < 0.001$) and 10-11 ($p < 0.01$). The noncontingent group presented a lower percent of opiate-positive urines than the control group during Weeks 8-9 ($p < 0.10$). The contingent and noncontingent groups also differed ($p < 0.10$) from each other in the average percent of opiate-positive urines presented at Weeks 8-9. Post-hoc analysis of the repeated measures effect using the Scheffe test indicated the control group presented a significantly ($p < 0.01$) greater percent of opiate-positive urines at the end of the intervention (Weeks 10-11) than they did prior to the intervention (Weeks 2-3). The noncontingent group also showed a significant ($p < 0.05$) increase in opiate-positive urine tests over this time. In contrast, the contingent group did not present a significantly higher percent of opiate-positive urines at Weeks 10-11 than at Weeks 2-3.

DISCUSSION

The results from this study suggest that contingent methadone-dose increases may be an effective means for reducing illicit-opiate use in outpatient methadone patients. The contingent group was clearly superior to the control group in presenting fewer opiate-positive urines, an effect that was most apparent during the middle of the detox when the clinic methadone dose was substantially reduced for the control group. The differences between the non-contingent and control groups were not as clear, but the trend for the former to present fewer opiate-postive urines was consistent. The differences between the noncontingent and contingent groups in the percent of

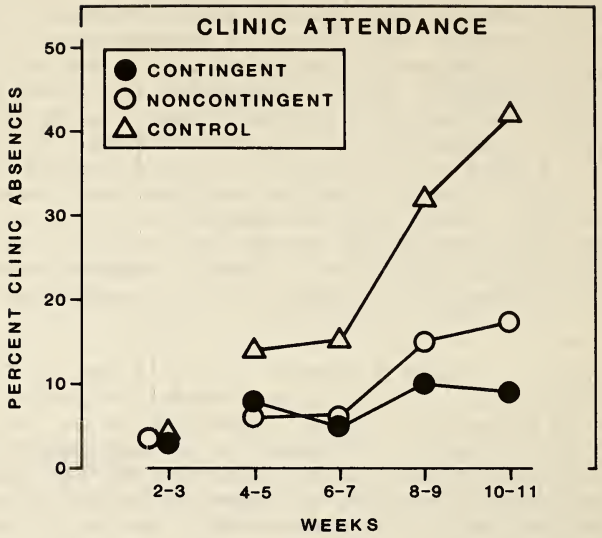

FIGURE 1. Average percent of missed clinic appointments during consecutive two-week study periods. Percentages are based on seven appointments per subject per week.

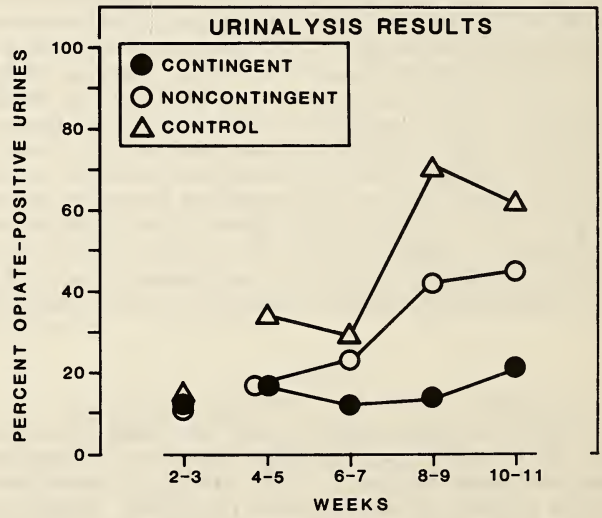

FIGURE 2. Average percent of opiate-positive urine tests during consecutive two-week study periods. Percentages are based on three urine tests per subject per week.

opiate-positive urines presented were only marginally significant at Weeks 8-9, but the trend was consistently one of the contingent group exhibiting greater treatment effects. This trend is particularly interesting because it implicates the conjoint role of the contingency and the pharmacological properties of methadone in reducing illicit-opiate use in the contingent group. In fact, more opportunities existed for noncontingent group members to obtain extra methadone than for members of the contingent group because noncontingent group members could do so even after providing opiate-positive urines. Basic research studies have demonstrated the reinforcing efficacy of methadone in nonhumans (Schuster & Balster, 1971) and in human opiate addicts (Stitzer et al., 1983c). The effects obtained with the contingent group in the present study illustrate how the reinforcing efficacy of methadone can be utilized to maintain abstinence from illicit-opiate use in opiate addicts.

The reinforcing efficacy of methadone was further suggested in the present study by the lower percentage of clinic absences in the contingent and noncontingent groups relative to the control groups. Although the maximum methadone-dose increase permitted (20 mg) is not particularly high for experienced opiate users, the availability of this amount of extra drug was sufficient to engender a higher rate of clinic attendance in the two dose-increase groups. Maintaining a high rate of clinic attendance is important not only for suppressing illicit-drug use, but also because clinic staff are provided a greater number of opportunities to counsel patients in psychiatric, employment, and other drug- and nondrug-related areas.

Although this study is still ongoing and the data are preliminary, the effects obtained to date are consistent with the existing literature showing the efficacy of contingency-management techniques in methadone treatment of opiate dependence. The use of contingent methadone-dose increases appears to have promise as a clinical method for reducing illicit-opiate use in outpatient methadone programs.

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Naltrexone in Addicted Physicians and Business Executives

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ABSTRACT

Naltrexone was administered to 114 opiate-dependent business executives and 15 opiate-dependent physicians as part of a comprehensive outpatient aftercare program following inpatient detoxification using clonidine. Over 80% of patients successfully completed at least six months of treatment without relapse or re-addiction and were still drug-free at 12-18 months follow-up. Patients who completed at least six months of treatment were more likely to be opiate free at follow-up than patients who had dropped out at an earlier point in the program. This study demonstrates that naltrexone can be an extremely useful and appropriate treatment for highly motivated middle/upper class addicts when administered within the context of an intensive high-expectation program.

INTRODUCTION

During the past two decades, opiate addiction has spread to the middle and upper class segments of American society. Contrary to established stereotypes, addicts now include many who are corporate executives, business owners, health professionals, and others who hold responsible jobs, earn substantial incomes, and do not commit crimes to obtain drug supplies. Unfortunately, the treatment needs of this addict subgroup are not adequately met by the existing publicly supported treatment system. Treatment with methadone or in methadone clinics is usually unacceptable to middle/upper class addicts and may be distinctly contraindicated in many cases because of the social stigma, identification by government agencies, and exposure to drug-related crime. Public drug-free programs pose similar problems. The typical middle/upper class addict desires complete abstinence and prefers treatment in a private setting.

We now report the successful use of naltrexone in addicted physicians and business executives who were treated in our intensive programs at Regent and Fair Oaks Hospitals. This study afforded a unique opportunity to evaluate the efficacy of naltrexone in ad-

dicts who were socio-economically advantaged, with valuable jobs or careers, and strongly motivated for treatment by a combination of internal and external factors.

METHODS

Patients

The patients in this study were admitted to Regent or Fair Oaks Hospital during the time period from February 1979 to February 1981. All had been addicted to opiates for at least two years. The subgroup of 114 business executives represent all opiate-dependent patients admitted during the specified time period who met the following criteria: (a) employed in a "white collar" job, family or self-owned business, or professional; (b) earning at least $20,000 per year; (c) successfully completed the inpatient treatment program and started outpatient aftercare treatment with naltrexone. The average age of this subgroup was 30 years, 92% were white males, and their average income was $42,000 per year. The subgroup of 15 physician addicts represent all opiate-dependent physicians admitted for treatment during the specified time period who successfully completed the inpatient program and started naltrexone aftercare. All were white males and their average age was 38 years.

Treatment Protocol

The first phase of treatment consisted of a 4-10 week inpatient program on a highly structured and intensive specialized unit at Regent or Fair Oaks Hospital. The inpatient program included initial detoxification using clonidine as well as daily participation in group therapy, individual therapy, peer group meetings, educational classes, and physical exercise. Where appropriate, the patient's spouse or family participated in joint meetings and in aftercare planning. All patients were inducted onto naltrexone during the final two weeks of inpatient treatment.

The inpatient program was presented to patients as the initial step in a longer term recovery plan designed to foster continued abstinence and address the psychological aspects of their addiction through changes in lifestyle, interpersonal relationships, and behavior patterns. In this regard, all patients signed an aftercare treatment contract before leaving the hospital stipulating naltrexone maintenance, group therapy, individual therapy, family/couples therapy, and drug abstinence verified by random urine checks for at least six months after hospital discharge.

RESULTS

Table 1 shows that 70 patients in the business executive subgroup completed at least six months of naltrexone treatment in the outpatient aftercare program. An additional 23 patients discontinued naltrexone before six months but remained opiate free and participated in the outpatient program for at least six months.

Table 1
ADDICTED BUSINESS EXECUTIVES
(N=114)

	Number	Percentages
Completed at least six months of naltrexone and therapy	70	61
Completed less than six months naltrexone, but stayed opiate free and in therapy for at least six months	23	20
Re-addicted or status unknown at six months	21	19

These patients were all drug free, employed, and functioning reasonably well when they discontinued the medication. Reasons for stopping the naltrexone included generalized concern about potential long-range health consequences, a felt need to remain opiate-free "on their own" without pharmacologic assistance, and side effects of stomach upset, sleeplessness, and nervousness that they attributed to the medication.

At 12-18 months, 64% of the 93 available patients were still opiate free and 36% were either known to be re-addicted or lost to follow-up. Those who had stayed in the program for at least six months on naltrexone and/or with drug-free urines were more likely to be opiate free at this point than those who had dropped out before six months.

Table 2 shows that in the subgroup of physician addicts, 11 patients completed at least six months of naltrexone treatment and an additional two patients discontinued naltrexone at an earlier point in treatment but nonetheless remained opiate-free and participated in the outpatient program for at least six months.

Table 2
ADDICTED PHYSICIANS
(N=15)

	Numbers	Percentages
Completed at least six months naltrexone and therapy	11	74
Completed less than six months naltrexone, but stayed opiate free in therapy for at least six months	2	13
Re-addicted, rehospitalized	2	13

The remaining two patients relapsed and required additional inpatient treatment. At 12-18 months, all 13 patients who had successfully completed at least six months of treatment were still opiate-free and continuing their successful return to medical practice.

DISCUSSION

Our findings demonstrate the highly successful use of naltrexone in motivated middle and upper class addicts suggesting that naltrexone may be the treatment of choice for such patients. Naltrexone retention rates in these patient subgroups were approximately two to five times greater than those reported in other studies (Hollister, 1978; Bradford et al., 1979). The relative success of our patients may be attributable in part to their being more socially and economically advantaged than most previous naltrexone research subjects and to the fact that they entered treatment with good job, career, and family supports. They had a great deal to lose by continuing their drug use and also had a history of being able to function well before their addiction to opiates. These motivational factors in combination with our highly structured, high-expectation program contributed to their overall success. This explanation is consistent with previous studies that have identified some of the favorable criteria associated with success in naltrexone treatment. For example, addicts with higher pretreatment levels of psychosocial functioning and those with non-drug-using spouses have shown better retention in naltrexone treatment (Resnick and Washton, 1978; Parwatikar et al., 1976). Similarly, programs that have administered naltrexone in conjunction with a high level of rehabilitative services (e.g., counseling, psychotherapy, urine screening) have usually produced greater retention and drug-free success rates (Stone-Washton et al., 1982; Hurzeler et al., 1976).

The length of time in naltrexone treatment appears to have an important influence on treatment outcome. For example, in a one-year follow-up study, Resnick and Washton (1978) found that whereas only 2% of 208 former naltrexone patients were still opiate-free following less than three months on naltrexone, 31% of 59 patients were opiate-free after 3-24 months of naltrexone treatment. Similarly, our data showed that patients who completed at least six months of naltrexone treatment were more likely to be opiate-free at follow-up than patients who dropped out of treatment shortly after hospital discharge. While compliance with naltrexone treatment may have contributed in part to our patients' success, the subgroup who discontinued naltrexone before six months but remained in the aftercare program was also successful. This finding suggests that for at least some of our patients the nonpharmacologic components of our structured aftercare treatment program (i.e., therapy, group meetings, urine checks) may have been more the crucial factors in determining outcome.

Naltrexone appears to be an especially useful and appropriate treatment for the physician addict. With the protection of nal-

trexone, the physician addict can return to the practice of medicine and continue the rehabilitative process despite recurrent life stress and continued access to drugs. We have found that hospital administrators, licensing boards, and other authorities responsible for the future of the physician addict tend to feel more comfortable about allowing the patient to resume medical practice when naltrexone is a mandatory part of the recovery plan. Our finding that 13 of 15 physician addicts (87%) successfully completed the outpatient program, re-entered medical practice, and were still drug free at one year follow-up compares very favorably with previous reports (Wall, 1958; Green et al., 1981; Modlin and Montes, 1984) showing that between 27% and 72% of physician addicts are able to resume their careers following treatment. While further work is needed to determine the best treatment for this subgroup of opiate addicts, the use of naltrexone should clearly be an important feature of the addicted physician's recovery plan.

Naltrexone appears to be a well-suited, well-tolerated, and well-accepted treatment for the motivated addict who is able to use the time previously spent on drug involvement on career development and lifestyle change. The recent FDA approval of naltrexone for marketed prescription use allows for the treatment of opiate addicts by private physicians and in private medical facilities, thus bringing the treatment of these patients further into the mainstream of medical practice. This may remove a significant obstacle to treatment for many middle/upper class addicts who otherwise prolong their addiction in the process of trying to avoid public treatment facilities.

FOOTNOTE

1. An earlier version of this manuscript was published in Advances in Alcohol and Substance Abuse, 4(2): 48-51, 1984, and is reprinted with permission of Haworth Press, Inc.

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Outpatient Methadone Detoxification: Effects of Diazepam and Doxepin as Adjunct Medications

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In recent years, there has been increasing interest and research in the use of adjunct medications during opiate detoxification. Although use of supplemental medications to control withdrawal symptomatology has received general clinical application for many years, there had been little systematic research in the area prior to reports of the significant anti-withdrawal effects of the alpha-2-adrenergic agonists clonidine and lofexidine (Gold et al. 1978,1980,1981; Washton and Resnick 1980).

The present adjunct medication study compared the effectiveness of doxepin and diazepam on a variety of outcome measures during outpatient opiate detoxification treatment. Clinically, anti-anxiety and anti-depressant medications, either prescribed by the program or illicitly obtained, are often used by detoxification clients to control withdrawal symptoms. Two factors would support the choice of these medications in this population. First, many of the symptoms associated with opiate withdrawal resemble those of anxiety and depression, including restlessness, sleep disturbance, muscle ache, fatigue, and irritability. Second, these medications have a relatively high safety level and a relatively low level of side-effects, making them particularly well suited for outpatient use.

The procedures in the present study differed from those generally used in other adjunct medication research in several important ways. First, the dosing schedule included both acute and chronic dosing regimens, designed to assess the effects of a range of doses on several dependent variables. Second, the adjunct medication regimen was superimposed on a gradual rather than an abrupt methadone detoxification schedule, allowing the assessment of the effectiveness of the adjunct medications in the most commonly used clinical procedure. Third, the present study utilized a wide variety of outcome measures, including continued illicit opiate use, other drug use, clinic attendance, adjunct medication refusal rate, and symptomatology.

METHODS

Subjects. Approximately 50 subjects were enrolled in a 90-day or 13-week outpatient detoxification. Subjects were eligible for detox on the basis of a documented history of opiate use and urinalysis evidence of current opiate use. During the first three weeks on the program, urine specimens were collected twice weeky on Mondays and Fridays and analyzed for the presence of opiates. Clients were selected for the present study if at least half of the specimens were opiate free. Approximately half of the enrollees met this criterion; the remaining clients either dropped out of treatment prior to study assignment or were assigned to an alternative study because of their high initial levels of illicit opiate use. Drug use was used as a selection criterion in this study since the effects of the pharmacological intervention could be obscured if subjects were chronically supplementing their methadone dose with additional opiate drugs.

Subjects averaged 30 years old, were generally single, separated, or divorced, and had worked 17 out of the last 24 months. Subjects reported an average of 4 to 7 years of continuous opiate use prior to this treatment enrollment. Although the diazepam group was significantly younger than the doxepin group, there were no other significant differences between the two study groups on demographic characteristics.

Procedures. All doses of methadone were mixed with a cherry syrup vehicle and administered under double-blind conditions by clinic nursing staff. All clients were stabilized on 40mg per day of methadone during the first three weeks of the study. The methadone dose was then decreased in 10mg steps at the beginning of weeks 4 and 5. This initial 20mg dose decrease was expected to engender measurable levels of symptomatology prior to the acute phase of the adjunct medication protocol. The methadone dose was further decreased 4mg per week over the next 5 weeks; subjects were then maintained on cherry syrup vehicle only for the final 4 weeks of the detox. Dosing for the adjunct medications was changed from acute to chronic when the methadone dose reached 4mg in week 9 of the detox.

At the beginning of week 5, subjects were randomly assigned to receive either doxepin or diazepam. Both drugs were dispensed in once-daily dosage forms, doxepin as Sinequan and diazepam as the sustained-release Valrelease. Capsules were available each day at the time of methadone administration. All medications were dispensed in opaque orange capsules under double-blind conditions. Subjects had the opportunity to decline each daily dose without influencing the future availability of the medication; however, if chosen, the capsules had to be ingested at the clinic under nursing supervision. During weeks 5 through 8, subjects were exposed to a dose range of either doxepin (0, 25, 50 and 75 mg) or diazepam (0, 15, 30 and 45 mg) in a random order. During this acute dosing phase, each dose was administered on two consecutive days

with at least a three-day placebo wash-out between active doses. Subjects were informed at the start of the acute dosing period that they would receive both active medication and placebo ("blanks") but that, as the detox continued, the frequency of active doses would increase.

Each day during weeks 9 and 10, subjects had the opportunity to ingest the intermediate dose of their assigned drug (diazepam 30mg or doxepin 50mg). At week 11 during this chronic dosing period, if subjects had reported an increasing level of withdrawal symptomatology without reports of significant side-effects from the study medication, the drug dose was increased from the intermediate dose to the high dose administered during the acute dosing phase (diazepam 45mg or doxepin 75mg). During the final week of the detox, the adjunct medication dose was decreased and then discontinued.

Several standard clinic procedures were used to collect data on the dependent variables. Daily attendance records were maintained by the clinic nurses; subjects were discharged when they missed three consecutive days at the program. Throughout the detox, all subjects provided urine specimens on Monday, Wednesday, and Friday. These specimens were tested using an on-site EMIT system for the presence of supplemental opiate drugs. Finally, all subjects completed symptomatology reports at each clinic visit.

RESULTS

Treatment retention was measured as the number of days subjects remained active in the clinic without missing three consecutive days. There was a significant difference between the two medication groups in the proportion of subjects who completed the 90-day detox. Specifically, 5 out of the 10 diazepam subjects but only 1 out of the 13 doxepin subjects successfully completed the 13-week detoxification protocol ($Z=2.29$; $p<.05$). Mean number of days in treatment was 74.1 days (S.D.=22.5) for diazepam subjects and 65.5 days (S.D.=17.9) for doxepin subjects. Although on the average diazepam subjects remained in treatment over a week longer than doxepin subjects, this difference is not statistically significant due to large within-group variability. Results for the remaining dependent measures are based on 8 out of the 10 diazepam subjects and 9 out of the 13 doxepin subjects who remained at the clinic for at least 9 weeks and entered the chronic dosing phase of the study.

Clinic attendance was similar in the two medication groups during the baseline and acute dosing phases of the study. During weeks 2 through 8, subjects in both groups missed 10% or less of their clinic visits. During the chronic dosing phase of the detox, the rate of missed clinic days increased in both groups; however, the "no show" rate was lower for diazepam subjects (13%) than for doxepin subjects (22%).

During both phases of the study, subjects in the diazepam group

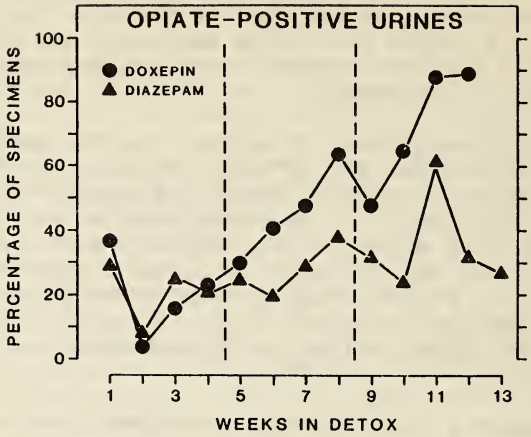

FIG. 1. Percentage of opiate-positive EMIT urine tests for doxepin and diazepam subjects during successive weeks in the detox. Data points represent the total number of opiate-positive specimens provided during each week divided by the total number of specimens possible (N X 3). Specimens missing as a result of subjects' not attending the clinic were treated as opiate-positive results. The broken lines following weeks 4 and 8 represent the introduction of the acute and chronic dosing periods for adjunct medications.

were more likely to refuse their capsules than were subjects in the doxepin group. Subjects in the doxepin group refused only three capsules out of all the occasions on which they were available. In contrast, subjects in the diazepam group refused approximately 20% of available capsules during the acute dosing phase of the detox and 13% during the chronic dosing phase.

The percentage of opiate-positive specimens for each treatment group throughout the detox is presented in figure 1. Less than 25% of specimens were opiate-positive during baseline weeks 2 - 4. Starting in week 5 at the introduction of the adjunct medications, rates of opiate-positive specimens diverged for the two treatment groups. During the acute dosing phase, the mean rate of opiate-positive test results was 46% for doxepin subjects and 28% for diazepam subjects. Rates of supplemental opiate use increased for both groups during the chronic dosing phase of the study when the methadone dose had reached 0mg; however, this increase was more dramatic in the doxepin group than in the diazepam group. The mean percentage of opiate-positive specimens increased to 63% for the doxepin group and to 37% for the diazepam group. The overall increase in the opiate-positive rate for diazepam subjects was in large part accounted for by the single-week increase in week 11 of the detox.

Withdrawal symptoms were measured using a 20-item self-report questionnaire on which each symptom was rated on a 10-point scale of increasing severity. Each subject's average symptom score during weeks 2 through 4 was subtracted from his mean symptom score during subsequent weeks to yield a difference-from-baseline symptom score for each subject during weeks 5 through 13 of the detox. These difference-from-baseline scores were averaged across subjects within each treatment group to provide a weekly mean difference-from-baseline symptom score for each medication group. There was a difference between the two medication groups in the patterning of symptomatology scores during both the acute and chronic phases of the study. Doxepin subjects reported no change from baseline in symptom scores during the 4-week acute dosing period; symptom scores then steadily increased during the chronic dosing phase when the methadone dose had reached 0mg. In contrast, diazepam subjects showed an immediate increase in symptoms at the start of the acute dosing period; however, symptom scores then remained relatively stable throughout the remainder of the detox.

DISCUSSION

Subjects assigned to the diazepam treatment group were more likely to complete detoxification treatment, attended the clinic more regularly and had fewer opiate-positive urine specimens than subjects assigned to receive doxepin during the detox. It is interesting that the diazepam group had a generally improved outcome in comparison to the doxepin subjects on several clinical indicators of treatment success despite their higher capsule refusal rate and their more rapid onset of withdrawal symptomatology complaints.

The high drop-out rate for doxepin subjects has made systematic comparison of the two groups difficult during the final two weeks of the detox. This comparison is of particular interest for the percentage of opiate-positive urine tests since the outcomes diverge most dramatically during the final weeks of treatment when methadone has been discontinued at the clinic. In earlier research at this clinic using a similar methadone detoxification protocol (McCaul et al. 1984), approximately 75% of specimens have been opiate positive during the last 2 to 3 weeks of the detox; this historical rate of opiate-postive specimens is appreciably above the diazepam group rate at the end of the current detoxification protocol.

The results of the present study indicate that diazepam administration during outpatient opiate detoxification may improve treatment outcome on several clinically important variables. Furthermore, experiences of the nursing and clinical staffs during this research suggest that adjunct medication administration can be well controlled in an outpatient setting with relatively few complaints of untoward incidents resulting from the study medication and relatively low risk of medication diversion by the study participants.

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Effects of a Dose Increase on Chronic Opiate Use During Methadone Detoxification

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The purpose of the present study was to evaluate the effects on illicit opiate drug use and treatment retention of administering high methadone doses during detoxification treatment to chronic opiate supplementers. The rationale for this treatment approach was based on previous reports which indicated that higher methadone doses are associated with less illicit opiate drug use during maintenance treatment (Gossop et al. 1982; Ling et al. 1976; McGlothlin and Anglin 1981) and on a previous uncontrolled study with chronic opiate supplementers which showed that opiate positive urine samples were reduced following a 20 mg blind dose increase (Stitzer et al. 1984). In the present study we planned to expose patients to methadone doses which would provide an adequate blockade of opiate drug effects while suppressing the withdrawal symptoms which might result from cessation of illicit drug use.

METHODS

Twenty-six male opiate-dependent subjects participated. Their average age was 29 years and they had been continuously addicted to opiates for an average of about eight years. Racial composition was 43 percent black and 57 percent white. Half (54%) of the subjects had been previously enrolled in methadone detoxification or maintenance programs, while half were new to methadone treatment. These subjects represent 25 percent of the 104 admissions to outpatient detoxification which occurred between January 1982 and August 1983 at the Behavioral Pharmacology Research Unit. Subjects selected for the present study showed more than 50 percent opiate-positive urinalysis test results during treatment weeks 2 and 3 when all detox patients were maintained on a stable methadone dose. Patients with 50 percent or fewer opiate positive urinalysis tests participated concurrently in other detoxification studies.

Procedure

Subjects were enrolled in a 90-day (13-week) outpatient detoxifi-

cation treatment program. Methadone dose was initially stabilized at 30 mg/day during treatment weeks 1 - 3. At the end of week 3, patients with more than 50 percent opiate-positive urine tests were randomly assigned to one of two blind dosing regimens. As shown in Table 1, subjects in the control group received 30 mg/day methadone from week 4 through week 10 of the detox; the dose was then reduced in 10 mg steps at the start of weeks 11, 12, and 13. Methadone dose in the experimental group was increased to 60 mg/day during study weeks 4 and 5. This dose was then lowered by 10 mg steps at the start of study weeks 6, 8, 10, 11, and 12. Thus, experimental subjects received doses at or above the original stabilization dose throughout week 10 of the 13-week detox.

TABLE 1. *Methadone Dosing Schedules*

	Methadone Dose (mg)	
Treatment Week	Experimental	Control
1	30	30
2	30	30
3	30	30
4	60	30
5	60	30
6	50	30
7	50	30
8	40	30
9	40	30
10	30	30
11	20	20
12	10	10
13	0	0

Subjects ingested methadone daily in a cherry syrup vehicle under nursing supervision. Doses were prepoured and delivered under single-blind conditions. Clinic attendance was not mandatory, but missed clinic visits resulted in missed medication opportunities. Urine samples were collected three times weekly (Monday, Wednesday, Friday) and analyzed for opiates using an on-site EMIT system (Syva Corp.).

Measures

Two treatment outcome measures were analyzed: 1) Treatment retention. Patients were terminated from treatment after missing three consecutive medication opportunities. The number of treatment days prior to termination provided the measure of treatment retention. 2) Opiate-positive urines. Percent of thrice weekly urine tests which were positive for opiate drugs on the EMIT system was determined for each treatment group during successive two week study periods. Missing samples were counted as opiate positive.

RESULTS

Treatment Retention

Substantial between-group differences in treatment retention are reflected in median durations of enrollment which were 86 days (I.Q. range = 50 - 90 days) and 41 days (I.Q. range = 28 - 86 days) for the experimental dose increase (N = 13) and control (N = 13) groups, respectively. This difference was not significant in a Mann-Whitney U Test. Average treatment retention was 68.3 days (SEM = 6.8 days) for the experimental group and 53.7 days (SEM = 7.0 days) for the control group. The between-group difference for average treatment days was also not significant ($t = 1.44$, $df = 24$, n.s.).

Opiate-Positive Urines

Urinalysis data were analyzed for the 11 experimental and 10 control subjects who remained in treatment through study week 5. During dose stabilization, experimental and control subjects averaged 80 percent and 87 percent opiate-positive urine tests, respectively. During study weeks 4 and 5, when experimental subjects were receiving 60 mg/day methadone and where the impact of the dose increase treatment was expected to be greatest, the percent of positive urine tests for the control group was unchanged (83% positive) while the percent of positive tests for the experimental dose increase group dropped to 62 percent. Although the between-group difference in number of opiate-positive tests was not significant in an analysis of covariance ($F = 1.9$, $df = 1,19$, $p < 0.20$), the experimental group did show a marginally significant decrease from their own baseline in opiate-positive urine tests (correlated $t = 2.39$, $df = 10$, $p < 0.05$).

Examination of individual subject data revealed that the treatment effect was primarily due to two experimental subjects who reduced their opiate-positive sample rate by more than 50 percent following the dose increase; none of the control subjects showed reductions of this magnitude. Overall, 6 of 11 experimental subjects (55%) and 3 of 10 control subjects (30%) delivered fewer opiate-positive urine samples during the two 60 mg dose increase weeks than during the preceding two dose stabilization weeks.

Five control and seven experimental subjects remained in treatment for 10 weeks or longer. This subgroup showed 75 - 80 percent opiate-positive urine tests during initial dose stabilization (weeks 2 and 3). Control subjects continued to deliver about 70 percent positive urine specimens throughout the 13 week treatment program. For the experimental dose increase group, opiate-positive tests decreased to 60 percent during study weeks 4 and 5 when their methadone dose was 60 mg/day, decreased further to 50 percent during weeks 6 and 7 when the methadone dose was 50 mg/day and then remained at about 50 percent through study week 11, at which time the methadone dose had decreased to 20 mg/day. Percent

opiate-positive tests rapidly increased for this group during the last two study weeks when the methadone dose was 10 mg or less, returning to the high levels observed during the initial dose stabilization portion of the study. Five of the seven experimental subjects who remained in treatment through week 10 showed a decrease in urine positive tests during this time. Specifically, these subjects reduced their opiate-positive urine test rate by at least 40 percent from their own baseline rate and maintained the reduction for at least four weeks during the intervention.

DISCUSSION

This study showed that raising the methadone dose to levels characteristic of maintenance treatment (50 - 60 mg/day) during the early weeks of a detox program resulted in improved treatment retention and decreased rates of opiate-positive urine test results in chronic opiate supplementers. Subjects in the experimental dose increase group remained in treatment for about two weeks longer on the average than did control subjects, while median treatment retention was twice as long for the experimental dose increase group (86 days) as for the control group (41 days), but neither difference was statistically significant due to within group variability. Since methadone appears to be a reinforcing drug for treatment patients (McCaul et al. 1982; Stitzer et al. 1983), longer treatment retention would be predicted for subjects who receive more methadone.

Opiate-positive tests were reduced by approximately 20 percent from control levels during the first two weeks of the dose increase treatment and the effect persisted throughout a substantial portion of the detox in a subgroup of patients who remained in treatment for 10 weeks or longer. These results are consistent with those from a previous uncontrolled study with chronic opiate users (Stitzer et al. 1984) in which dose was raised from 30 mg to 50 mg per day for two weeks during the initial phase of detox treatment and also consistent with differences in opiate-positive urine rates reported for maintenance patients on higher versus lower doses of methadone (McGlothlin and Anglin 1981).

Although the dose increase procedure had a noticeable impact on opiate-positive rates, the clinical importance of the reductions noted is questionable. The effect was small in magnitude and inconsistent across subjects. For example, only two subjects showed a substantial initial reduction in opiate-positive rates following the dose increase and only five of the original thirteen subjects benefitted at any point. More importantly, the experimental subjects as a group were delivering 50 - 60 percent opiate-positive urines throughout the detox. It can be argued that this positive urine test rate still represents a substantial amount of continuing illicit opiate use. Thus, it appears that a substantial methadone dose increase given in the context of detoxification treatment does not have a sufficiently large effect on illicit opiate use of chronic opiate supplementers to be by itself a clinically useful procedure.

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Assessment and Extinction of Conditioned Withdrawal-Like Responses in an Integrated Treatment for Opiate Dependence

Anna Rose Childress; A. Thomas McLellan; and Charles P. O'Brien

INTRODUCTION

Wikler's (1948) original observations of opiate withdrawal-like responses in drug-free patients have stimulated almost four decades of research on opiates and Pavlovian conditioning processes (O'Brien et al. 1983). The results of this work indicate that conditioned withdrawal-like and opiate-like responses occur in both animals and humans (Eikelboom and Stewart 1979; Grabowski and O'Brien 1980). Addict patients often experience drug craving and/or withdrawal-like changes in skin temperature, pupillary dilation, etc., in response to drug-related slides, videotapes (Teasdale 1973; Sideroff and Jarvik 1980) or cook-up paraphernalia (Ternes et al. 1979). Our own research has demonstrated that opiate withdrawal-like responses in humans can be conditioned to an arbitrary conditioned stimulus (O'Brien et al. 1977).

From this accumulated evidence it seems clear that conditioned withdrawal-like phenomena exist, but their actual incidence and clinical importance remain controversial. Wikler (1948) felt that conditioned withdrawal-like responses constituted a common 'disease de novo' in opiate addicts, and a primary cause of relapse. This view has been challenged by recent interview data (McAuliffe 1982) suggesting that conditioned withdrawal-like phenomena are relatively uncommon and seldom lead to opiate use/relapse.

Our research center (O'Brien et al. 1983) is currently developing a set of procedures 1) to determine the actual incidence of conditioned withdrawal-like phenomena in opiate-dependent patients, 2) to attempt extinction of these responses, and 3) to examine their postulated role in clinical outcome, including relapse (Wikler 1948). At the previous Proceedings (Childress et al. 1983) we reported preliminary results of our attempts to measure and to extinguish conditioned withdrawal-like responses in several pilot patients. The current paper updates those findings and discusses several methodological changes which we feel will permit more accurate assessment of these responses, more effective extinction, and thus, a more meaningful evaluation of their contribution to clinical outcome in our patients.

METHODOLOGY

Design Considerations - In our initial attempt to elicit and to extinguish conditioned withdrawal-like responses (O'Brien et al. 1979) we asked patients maintained on an opiate antagonist (Naltrexone) to undergo double blind cook-up and unreinforced self-injection rituals. Opiate administration was either omitted (saline trials) or pharmacologically blocked due to the antagonist treatment. Though cook-up and self-injection stimuli were potent elicitors of withdrawal-like responses, the procedure itself produced such strong dysphoria, withdrawal and craving that most patients refused to participate after only a few trials. Even though no subject completed extinction, there was some suggestion that patients who completed more trials had somewhat better outcomes at six-month follow-up than other non-extinction Naltrexone patients (O'Brien et al. 1979).

For our next extinction attempt (the current protocol) we tried to modify the earlier procedure in ways that should increase patient comfort and compliance: 1) patients were given early trials with series of drug-related stimuli as a prelude to the highly evocative cook-up and self-injection ritual; 2) each extinction trial was followed by 15 minutes of deep relaxation training to allow the patient to 'wind down' from any discomfort or craving triggered by exposure to the drug related stimuli.

As another consideration, we recognized that an extinction procedure--even if well-tolerated by patients--would address only the conditioned factors of their disorder. If the significant psychological, social and vocational components of the addiction were left untreated, the possible clinical benefits of the extinction could be overshadowed and perhaps not even measurable. With this in mind, we decided to integrate our laboratory-derived extinction procedure with professional psychotherapy, a clinical treatment which would address the non-conditioned features of the addiction and which had previously produced pervasive therapeutic benefits for our clinical population (Woody et al. 1981).

Subjects - The subjects for this ongoing study are male veteran methadone patients from the Drug Dependence Treatment Unit of the Philadelphia Veterans Administration Medical Center. Patient volunteers are recruited through direct contact or referral from their drug counselor. All patients are clinically screened to rule out diagnosis of major thought disorder (schizophrenia) or organic brain syndrome. Patients who are diagnosed as having only anti-social personality disorder (in addition to their drug dependence diagnoses) are also screened from the study, since such patients were previously found unresponsive to psychotherapy (Woody et al. 1981).

Procedure - Patients eligible for the study are randomly assigned to one of three treatment groups. The clinical outcome of patients receiving cognitive-behavioral psychotherapy, extinction, and relaxation (CE group) will be compared against two control groups: one group receiving therapy and relaxation, but no extinction (CT

group), and a standard treatment control group which receives extra drug counseling and educational/control materials (DC group). Professional attention, session length, and small payments contingent upon session attendence are equivalent for all treatment groups.

Laboratory Measurement of Conditioned Withdrawal-Like Responses - Prior to treatment, at the end of treatment, and at 1 and 6 month follow-up points, each patient's conditioned withdrawal-like responses are assessed in laboratory measurement sessions. All laboratory sessions are conducted in an enviornmentally-controlled, electrically-shielded recording chamber. Physiological measures include skin temperature, galvanic skin resistance (GSR, a general arousal index), heart rate, respiration and blood pressure. These physiological measures (except blood pressure) are continuously recorded on a polygraph and then converted to computer storage for later analysis.

In addition to the physiological measures, patients are asked to rate the degree of subjective high, craving or withdrawal they experience in response to test stimuli.

Both physiological and subjective responses are measured under two types of stimulus conditions: Neutral and Drug-Related. Each patient experiences both conditions, acting as his own control. For either stimulus condition, the following sequence obtains; lasting approximately one hour: 1) Resting Baseline; 2) Videotape (Neutral or Drug-Related); 3) Baseline; 4) Activity (Neutral or Drug-Related); and 5) Baseline.

The neutral videotape features a nature story, the neutral (the drug-related) activity allows patients to play a computerized "pong" game. The drug-related videotape features a cook-up-shoot-up ritual; the drug-related activity requires patients to go through a mock cook-up and tie-off, with optional self-injection of saline. Previous research in our center has shown pre-injection (drug preparation and cook-up) stimuli to be powerful elicitors of conditioned withdrawal-like responses (Ternes et al. 1979).

Extinction - Each hour-long treatment session for patients in the extinction group begins with 30 minutes of psychotherapy, followed by approximately 10 minutes of exposure to extinction stimuli. Each session ends with 15-20 minutes of relaxation, guided by audio cassette. Extinction stimuli include self-produced verbal imagery ("drug stories"), audiotapes of drug talk, color slides of cook-up-shoot-up rituals, videotapes of drug purchase, cook-up and injection, and finally, handling of drug objects in a mock cook-up/tie-off procedure. With exception of the self-produced 'drug-stories', extinction stimuli are not individualized, but are the same for all patients. Saline self-injection, the final member of the extinction series, is encouraged but optional. For each patient, the ordering of extinction stimuli across sessions is the same, and we employ a fixed trials procedure which determines the number of exposures to each stimulus category.

Data for the extinction trials is currently based on the Within-Session Rating Scale (1982), a quantified subjective report listing 24 withdrawal-like and 24 high-like symptoms. The WSRS is administered before and immediately after exposure to the extinction stimuli. We have begun to record skin temperature during treatment sessions, which will allow us eventually to track the course of extinction across sessions and to compare subjective with physiological responses.

Extinction sessions for outpatient subjects are conducted three times weekly, with 32 sessions comprising a complete course of treatment. We have also begun the same study with inpatients undergoing gradual methadone detoxification over a four-week period. For these inpatients, extinction trials are conducted five times weekly, for a total of 22 treatment sessions.

Daily methadone is administered immediately after measurement or extinction sessions so that its onset effects will not interfere with physiological or subjective measures.

Clinical Outcome Measures - Prior to treatment, at the end of treatment and at 1 and 6 month follow-up points, each patient is given a series of inventories to assess clinical status, psychiatric complaints, drug use and problems associated with the drug use. The following clinical measures are used: 1) Addiction Severity Index (McLellan et al. 1978); (2) Beck Depression Inventory (Beck and Beck 1972); (3) Hopkins Symptom Check List-90 (Derogatis et al. 1974). These instruments and their use as outcome measures is more fully described elsewhere (Woody et al. 1981).

RESULTS

Pretreatment Laboratory Measurements - Data from the pretreatment laboratory sessions is based primarily on 25 additional patients who have entered treatment since our initial report (Childress et al. 1983).

Physiological - In measurement sessions, patients continue to respond to drug-related stimuli with a variety of physiological responses, including an increase in arousal (a decrease in GSR) and transient, non-specific changes in heart rate and respiration. A time-linked decrease in skin temperature has remained the most reliable and specific index of a conditioned withdrawal-like response. Analyses of variance performed on the group data ($n = 25$) showed an overall statistically significant effect ($p < .001$) of interval (neutral vs. drug-related stimuli) upon skin temperature. The overall average decrease in skin temperature to drug related stimuli is approximately $4^{o}F$. As before, about a third of our patients, "responders," show marked decreases in skin temperature (often greater than the 4^{o} average) which seem specific to drug-related stimuli.

Similar to our preliminary findings, approximately one third of our recent patients are 'non-responders'--they show little or no temperature reduction to standardized drug-related stimuli in the laboratory setting. The remaining patients are more difficult to

characterize, but several fall into the category of 'non-specific arousers', showing mild arousal patterns to both neutral and drug-related activities, but no differential response in skin temperature or the other physiological measures.

Subjective - About 50% of the patients report increased craving to the standard drug stimuli, and 20% report actual subjective withdrawal. These figures are similar to our pilot data, but somewhat higher. There is a modest positive correlation ($r = .25$) between subjective reports of craving and reports of withdrawal. Only a few patients (8%) report increased subjective high to drug-related stimuli during pretreatment laboratory testing.

Though subjective craving is modestly correlated with skin temperature (physiological change) ($r = .23$), subjective withdrawal is not well correlated with skin temperature change ($r = -.06$, not sig.).

Extinction - Of 16 patients randomly assigned to the Extinction (CE) group, 8 completed 20 or more extinction trials. The extinction data presented here are based on these 'treatment completers'.

Subjective Craving - As shown in Figure 1, patients in the extinction (CE) treatment group show an initial increase in craving (following presentation of drug-related stimuli) which tends to diminish with repeated extinction sessions. The overall reduction in craving in the extinction group across sessions is statistically significant ($p < .001$). The amount of craving experienced by the extinction patients is significantly greater ($p < .001$) than that reported by patients in the other treatment groups who are not exposed to drug-related stimuli (see DC control group in Figure 1).

Subjective Withdrawal - Patients in the extinction sessions experience a significant increase ($p < .001$) in subjective withdrawal-like symptoms to the drug-related stimulus presentations, and they experience significantly more withdrawal-like symptoms than patients in treatment groups who do not receive exposure to drug-related stimuli. Withdrawal-like symptoms are relatively persistent in some patients, particularly those who occasionally give themselves 'conditioning' trials with illicit opiates. There is no significant overall reduction in withdrawal symptoms over trials, though about half of our 'responders' do show relatively complete extinction of subjective withdrawal-like symptoms within the allotted treatment sessions.

With use of less evocative stimuli as a prelude to cook-up trials, patients have been able to tolerate the procedures quite well and none left the study due to withdrawal discomfort.

Subjective High - Extinction patients occasionally report an increase in subjective high in response to drug-related stimuli, but there is no statistically significant pattern among treatment groups or across trials.

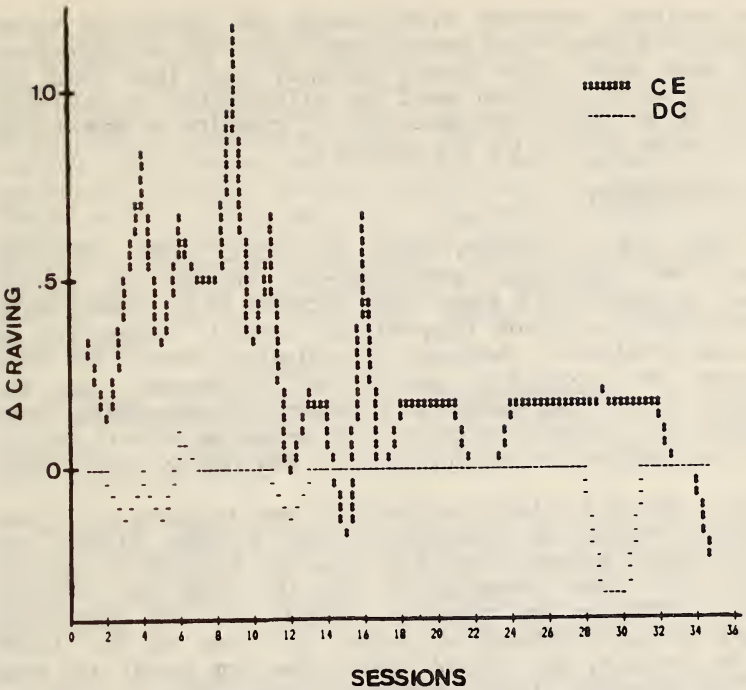

FIGURE 1. Reduction in craving to drug-related stimuli as a function of repeated exposures across sessions in patients given extinction (CE). Note reemergence of craving when cook-up rituals are begun, in session 16.

Post-treatment Laboratory Testing

Physiological- Taken as a group, the extinction patients show moderate attenuation of the initial skin temperature response following extinction ($6^{o}F$ decrease pre-treatment, $2^{o}F$ decrease post treatment). Patients in the control groups do not exhibit any systematic change in the temperature response.

Subjective - Craving is reduced to 0 in 80% of the extinction patients, suggestive of extinction. This pattern is not seen in the therapy-but-no-extinction comparison group.

Clinical Outcome - Based on analyses of variance performed on data from the ASI and psychiatric rating scales, all treatment groups are showing improvements at 6 month follow-up points, but improvement is greater in the two groups receiving professional psychotherapy. The pattern of improvements in the two therapy groups (decreased psychiatric symptoms, etc.) is similar to that found in our previous studies of psychotherapy with opiate-dependent patients (Woody et al. 1981), but less pronounced. At this juncture there is no significant difference in outcome

between patients receiving psychotherapy and extinction versus those receiving therapy and control activities, but no extinction. As discussed below, this result probably says less about the benefits of extinction than about the difficulties of developing an effective extinction procedure and of choosing an appropriate design in which to test for its effects.

SUMMARY AND COMMENTS

Recent data have generally been consistent with our pilot findings: a significant proportion--33 to 40%--of opiate-dependent patients show a time-linked decrease in skin-temperature in response to standard drug-related stimuli, suggestive of conditioned withdrawal. Patients' physiological changes are often accompanied by subjective craving and withdrawal, but the correlation among these measures is modest. Though craving seems to diminish with repeated exposure to drug-related stimuli, withdrawal-like symptoms are often persistent and slow to extinguish.

Our current design initially assumed that most patients would show conditioned craving and withdrawal to our standard stimuli and that our current procedure would be adequate to produce complete extinction for these 'responders.' As it turned out, not all patients respond to our standard stimuli, and our extinction procedure is not completely effective for those who do. Given these two findings, our current design does not permit the best test of the potential clinical benefits of extinction.

Our rich experience during the first phase of this project has stimulated several procedural changes which should increase our accuracy in determining the incidence of these conditioned phenomena, our effectiveness in extinguishing them, and permit a better assessment of their potential clinical benefit. These are as follows:

1) Individualize eliciting (drug-related) stimuli - We initially chose to use standard (the same for all patients) stimuli for practical and experimental reasons. However, their use may have resulted in an underestimate of the incidence of conditioned craving and withdrawal, and in less relevant extinction for many patients. Our experience now suggests that some of the most powerful conditioned stimuli may be individualistic - e.g., a patient may experience extreme craving at the sight of a paycheck stub. In the next phase of our study, the patient and therapist will select a group of individualized drug-related stimuli and incorporate them into the extinction series.

Earlier in the project we briefly considered a design change that would pre-select 'responders' to standard stimuli and then assign them to the current treatment groups, including extinction. However, this approach would fail to address - or even discover - conditioned craving and withdrawal which may be elicited by individualized stimuli.

2) Incorporate mood-related stimuli - In the course of our study we observed that many apparent 'non-responders' may exhibit craving or conditioned withdrawal-like symptoms in response to drug stimuli if they are tested in a certain emotional state (i.e. anxiety, depression, etc.). We now suspect that, for some patients, mood states may have become an integral part of the conditioned stimulus complex which elicits craving/withdrawal (Poulos et al. 1981), and that drug-related stimuli alone are sometimes insufficient to elicit the complete conditioned response. Effective extinction might necessitate trials administered while the patient is in problematic mood states (perhaps induced by suggestion) which help trigger craving/withdrawal.

3) Increase the number of extinction sessions to allow for relatively complete extinction. A trials-to-criteria format may be useful if individual variability is too great to permit a fixed trials procedure.

4) Assess the impact of adding extinction to drug counseling, not just psychotherapy. Under the possibility that extinction can add measurable benefits to the treatment of the opiate-dependent patient, it would be important to develop this procedure in a way that can be used in a number of standard treatment settings.

5) Employ an abstinent patient population - Since the presence of methadone (or any opiate) can attenuate the expression of conditioned withdrawal-like responses, it would be very informative to assess and to attempt extinction of these responses in a drug-free population. Though drug-free patients are usually difficult to retain in treatment, this population offers the most appropriate opportunity for determining the contribution of conditioned responses to relapse from an abstinent state.

With these procedural modifications, we anticipate a fuller understanding of the nature of conditioned craving and withdrawal and a better assessment of the role of these responses in opiate use and relapse.

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Benzodiazepine Dependence of Several Years Duration: Clinical Profile and Therapeutic Benefits

Forest S. Tennant, Jr., and Edward A. Pumphrey

ABSTRACT

Twenty-two (22) patients with long-term benzodiazepine dependence ranging from 3.5 to 13 years (Mean 7.4 years) were referred to us for evaluation and treatment. Daily dosages ranged from 10 to 100 mg (Mean 43.8 mg) of diazepam or its equivalent. Psychiatric diagnosis by DSM-III criteria revealed that 13 (59.1%) had schizophrenic disorder; 7 (48%) had generalized anxiety disorder, and 2 (9.1%) had manic depression. Only one patient could be totally withdrawn and remain abstinent from benzodiazepines without substituting another psychotherapeutic drug. Benzodiazepine dependence appeared therapeutic in the majority of these patients since psychotic symptoms, anxiety, or alcohol abuse were reduced. Based on these observations and other studies, we suggest that long-term benzodiazepine dependence should not always be discontinued, since the patient may have severe underlying psychiatric and medical illnesses that are therapeutically well controlled.

INTRODUCTION

Benzodiazepine dependence has been recognized in recent years.[1-3] There is, however, considerable uncertainty as to why this condition occurs and how it should be clinically managed. Some recent reports suggest that select patients therapeutically benefit from long-term dependence upon benzodiazepines, while others show that there may be an abuse problem among populations who misuse a variety of other drugs and alcohol.[4-10] Most reported cases of benzodiazepine dependence have occurred with high, daily dosages, although some reported cases have taken doses at or near normal therapeutic dosage ranges.[11,12] Another area of uncertainty has been whether symptoms observed after cessation of dependence always represent true withdrawal symptoms, or a recurrence or exacerbation of symptoms that existed prior to initiation of use.[2,4] Reported here is a study of 22 consecutive patients who

were referred to us with benzodiazepine dependence of 3.5 to 13 years duration. These patients were evaluated to identify underlying psychiatric and medical conditions. Attempts were made to withdraw some patients, and all were followed for periods ranging from 6 to 24 months to assess outcome. Observations of these patients suggest etiologic reasons for long-term benzodiazepine dependence and provide some guidelines for clinical management of this condition.

METHODS

Each patient was given a complete physical examination, health questionnaire, drug history, and a psychiatric assessment based on the Diagnostic Statistical Manual of the American Psychiatric Association, 3rd Edition (DSM-III). Specific inquiry was made as to previous psychiatric treatments, attempts to withdraw from benzodiazepines, alcohol abuse, reasons for beginning benzodiazepine use, and whether the patient wanted to attempt withdrawal. Whenever possible, previous medical records were obtained for review and family members were interviewed. A urine sample was collected and analyzed by immunoassay to document that benzodiazepines were being used, and an alcohol breath test was done on each patient.[13] Patients who desired to withdraw were administered propanolol, phenobarbital, and/or hydroxyzine over a period of 30 days in a manner described in other studies, or they entered into a schedule of progressive, declining dosages of benzodiazepines.[8,14,15] Patients who did not desire to withdraw were maintained with their benzodiazepine of choice after they signed a written consent form which described the risks and benefits of long-term dependence. During the first 30 days of evaluation and treatment, patients were seen two to five times per week for the purposes of medication adjustment and assessment of psychiatric status. After this period, each patient was followed at least every 30 to 90 days by telephone communication, regular clinic visits, and/or consultation with the referring physician. In those patients who totally withdrew, various psychotherapeutic medications were administered depending on which specific psychiatric symptoms were present.[13] Benzodiazepine abstinence was documented by urine test analysis.

RESULTS

This group of patients presented a clear profile of significant psychiatric and medical disease, as well as social difficulties. (Tables 1,2) Only 5 (22.8%) were employed and 7 (31.8%) were married. Medical records, self-report history, and/or family interviews documented that the majority had experienced previous psychiatric hospitalization (14; 63.6%) and psychotic episodes (13; 59.1%). Previous alcohol abuse and suicide attempts were reported by 7 (31.8%) and 6 (27.3%), respectively. Patients in some cases had a poor recollection and/or understanding as to why they originally started benzodiazepines, and the following were

given as reasons: "nervous", 7 (31.8%); "stress", 4 (18.2%); "nervous breakdown", 3 (13.6%); "help cope", 3 (13.6%); medical problem, 3 (13.6%); and unknown, 2 (9.1%). The three benzodiazepines used in descending order of frequency were diazepam, lorazepam, and chlordiazepoxide (Table Three). Diazepam dosages ranged from 10 to 100 mg per 24 hours (Mean 43.8; SD 29.1). Patients reported using benzodiazepines from 3.5 to 13 years (Mean 7.4; SD 3.72). The longest period of abstinence within the overall period of use which was reported by a patient was six months. Current use of benzodiazepines was confirmed in all patients by urine testing. All patients had previously attempted to totally withdraw only to resume use following discharge. Twelve (12; 54.5%) desired to withdraw at the time of our initial evaluation. Review of medical records and interviews of patients and family members indicated that the following psychiatric illnesses were present by DMS III criteria: schizophrenic disorder 13 (59.1%); generalized anxiety 7 (31.8%); and manic-depression 2 (9.18%) (Table Two). Patients had a wide variety of medical conditions and were taking a variety of therapeutic agents. Four (18.2%) indicated that they were currently abusing alcohol. Of the 12 patients who attempted withdrawal, three (3; 25.0%) desired to restart benzodiazepines within 10 days (Table Four). Six of the nine (66.7%) who withdrew developed psychotic symptoms, and three required hospitalization to control hallucinations and/or delusions. Three of these six did not develop psychotic symptoms until they were abstinent 30 days or more. Eight of the nine (88.9%) who completely withdrew required, within 90 days, administration of an antidepressant or antipsychotic agent, or the reinstitution of a benzodiazepine to control symptoms.

DISCUSSION

The clinical profile of patients studied here exhibits a variety of many serious psychiatric and medical conditions. There was no support found for the sometimes popular notion that normal, healthy individuals become dependent on benzodiazepines.[16-18] Found among these patients were long histories of psychotic illness, suicide attempts, psychiatric hospitalization, alcoholism, medical conditions, and social instability as evidenced by a relative lack of marriage stability and employment. A high percentage of these patients (10 of 22; 45.5%) did not desire to even attempt withdrawal because they believed that benzodiazepines were essential for adequate mental and social function. A recent study shows that normal adults, when given diazepam and placebo under blind conditions, prefer placebo.[19] Epidemiologic surveys show that less than 2% of persons prescribed a benzodiazepine continue to use it for more than one year.[20] Patients who choose to take benzodiazepines for very long periods, such as the ones in this study, should, therefore, be viewed as a special subgroup who probably have chronic psychiatric illness and who may likely benefit from benzodiazepine dependence. An important finding in this group of patients was the large number who had documented

histories of psychotic illness and who, by clinical evaluation, met DSM-III criteria for schizophrenic disorder. Six of nine (66.7%) patients who attempted withdrawal developed psychotic symptoms within 90 days, and three required hospitalization to control symptoms. Psychotic symptoms have previously been reported to occur during benzodiazepine withdrawal and they have generally been believed to simply be a part of a withdrawal syndrome.[22-23] Three of our patients did not develop psychotic symptoms until after 30 or more days of benzodiazepine abstinence, so it is very unlikely that their symptoms were related only to a withdrawal syndrome. It is, therefore, possible that at least some previous reports of psychosis following benzodiazepine withdrawal represent recrudescence of an underlying psychiatric disorder, or they are individuals prone to psychosis that is triggered by withdrawal.

There have been a number of recent studies which show that benzodiazepines can control psychotic and manic symptoms in many patients just as they appeared to do in some of our cases.[26-30] Benzodiazepines have proven effective enough in schizophrenia that some are now calling for reassessment of their use in treatment of this illness.[31] Considering the notorious side-effects of hepatitis, extrapyramidal effects, and tardive dyskinesia which frequently result from use of phenothiazines and neuroleptics, the benzodiazepines, with their low incidence of side effects, may be a preferable alternative for control of schizophrenia and mania in many patients. Some patients in this study were apparently never recognized as schizophrenic, but they empirically discovered that benzodiazepines could control their symptoms. This study and others on benzodiazepine withdrawal provide some clinical guidelines for treatment of the patient who has taken benzodiazepines for a long period. Tyrer and Owen attempted to withdraw patients who were taking therapeutic doses of diazepam for three months.[15] They found that gradual tapering of the daily dose over a 12-week period was successful for many patients, although some patients experienced enough psychiatric symptoms that withdrawal could not be accomplished. Most patients reported here took much higher doses of benzodiazepines for several years. In addition, they appeared to therapeutically benefit since psychosis, mania, anxiety, and alcohol abuse were reasonably well controlled. If withdrawal is to be attempted in a patient who has taken benzodiazepines for a very long period, it should be done gradually with the realization that continued administration of benzodiazepines may be therapeutically required to adequately control underlying psychiatric illness.

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TABLE ONE

DEMOGRAPHIC AND HISTORICAL CHARACTERISTICS

OF PATIENTS WITH LONG-TERM BENZODIAZEPINE DEPENDENCE

N = 22

	No.	
Female	15	(68.2%)
Male	7	(31.8%)
White	21	(95.5%)
Employed	5	(22.8%)
Married	7	(31.8%)
No. With Previous Psychiatric Hospitalization(s)	14	(63.6%)
No. With Previous Psychotic Episodes	13	(59.1%)
No. Who Have Attempted Suicide(s)	6	(27.3%)
Smoke Cigarettes	14	(63.6%)
Alcohol Abuse in Past	7	(31.8%)
No. Previously Attempted Inpatient Benzodiazepine Withdrawal	6	(27.3%)
No. Desired Withdrawal From Benzodiazepines	12	(54.5%)

TABLE TWO

CLINICAL PROFILE OF

LONG-TERM BENZODIAZEPINE DEPENDENCE PATIENTS

N = 22

Psychiatric Diagnosis by DSM-III Criteria		
Schizophrenic Disorder	13	(59.1%)
Generalized Anxiety Disorder	7	(31.8%)
Manic Depression	2	(9.1%)
No. Who Reported Current Alcohol Abuse	4	(18.2%)
No. Who Currently Used Additional Psychotherapeutic Drugs	6	(27.3%)
No. With a Concurrent Medical Condition		
Hypertension	5	(22.8%)
Gastrointestinal Disease	5	(22.8%)
Musculo-Skeletal Disease	4	(18.2%)
Obesity	4	(18.2%)
Dermatologic Disease	2	(9.1%)
Respiratory Disease	2	(9.1%)
No. Who Currently Used Medication(s) For a Medical Condition	10	(45.4%)

TABLE THREE

BENZODIAZEPINE AND DOSAGES USED IN DEPENDENCE

N = 22

Length of Dependence (Range in Years)	3.5-13
Mean Length Dependence (Years)	7.4 (SD 3.7)
Drug of Dependence	
Diazepam (No.)	16 (72.7%)
Dosage Per Day (Range in mgs)	10-100
Mean Dosage Per Day (mgs)	43.8 (SD 29.1)
Lorazepam (No.)	4 (18.2%)
Dosage Per Day (Range in mgs)	4-30
Mean Dosage Per Day (mgs)	11.0 (SD 12.7%)
Chlordiazepoxide (No.)	2 (9.1%)
Dosage Per Day (Range in mgs)	20-100
Mean Dosage Per Day (mgs)	60 (SD 56.6)

TABLE FOUR

OUTCOMES OF 12 PATIENTS

WHO ATTEMPTED WITHDRAWAL*

	No.	
Attempted Withdrawal But Restarted Benzodiazepines Within 10 days	3	(25.0%)
Completed Withdrawal But Developed Psychotic Symptoms Within 30 Days	3	(25.0%)
Completed Withdrawal But Developed Psychotic Symptoms Within 30 to 90 Days	3	(25.0%)
Completed Withdrawal But Developed Anxiety Symptoms Within 30 to 90 days	3	(25.0%)
Completed Withdrawal But Began Alcohol Abuse Within 30 Days	3	(25.0%)
Completed Withdrawal But Required Restarting Benzodiazepines or Other Psychotherapeutic Drug to Control Psychosis, Anxiety, and/or Alcoholism	8	(66.7%)
Completed Withdrawal and Not Taking Any Medications at End of 90 Days	1	(8.3%)

* Numbers add to more than 12 since some patients experienced more than one type of outcome.

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Due to space limitations, a complete list of references may be obtained from the senior author.

The Addiction Severity Index in Three Different Populations

A. Thomas McLellan; Lester Luborsky; Charles P. O'Brien; Harriet L. Barr; and Frederick Evans

INTRODUCTION

During the past ten years, our research group[1] has evaluated a number of different treatments for both alcoholism and drug addiction. Using a comprehensive evaluation instrument developed at our center (McLellan et al, 1980), we have concluded "that alcohol and drug abuse treatments can produce significant, pervasive and substantial positive changes..." (McLellan et al., 1982, p. 1427) not only in the target problems of alcohol and drug use, but in the important ancillary problems of employment, criminal behavior, and psychiatric symptomatology; i.e., his "psychiatric severity" based on a structure admission interview (McLellan et al., 1983, p. 624).

As a test of generality of our earlier conclusions with the male veterans, the present study was undertaken in three other Centers selected for diversity of their patient populations, using the same instruments and procedures developed for our previous studies. We had previously performed an extensive evaluation of our assessment instrument (the Addiction Severity Index) in these samples and had concluded that it was both reliable and valid for general use. This report will be presented in two parts, each focusing on an important evaluation issue within the field of substance abuse treatment:

1. Do patients admitted to these centers show improvement following substance abuse treatment? Are these improvements comparable to those seen in our earlier studies of male veterans?

2. To what extent are the outcomes from these treatments predictable from pre-treatment information? What type of information is most predictive among treatment centers and among various segments of the patient population?

Three treatment centers participated in this research:

Philadelphia VA Substance Abuse Treatment Unit - offers methadone maintenance, narcotic antagonist, drug-free outpatient and/or abstinence-oriented therapeutic community treatment to eligible male veterans.

Eagleville Hospital and Rehabilitation Center - is located twenty-five miles from Philadelphia and offers abstinence-oriented therapeutic community treatment to alcohol- and drug-abusing patients in a combined residential setting.

Carrier Clinic - a psychiatric treatment facility located twelve miles from Princeton, New Jersey; all treatment is inpatient, abstinence-oriented, therapeutic community.

All three programs offer a number of ancillary support services to substance abuse patients and are approved by the Joint Commission on Accreditation of Hospitals.

Subjects - A total of 181 voluntary subjects were recruited from the three Centers at the time of their admission to treatment. Fifty-seven male, drug-dependent subjects were recruited from the Philadelphia VA. Sixty subjects participated from the Carrier Clinic; 15 female alcohol, 22 male alcohol, 15 female drug and 9 male drug-dependent. Sixty-four subjects participated from the Eagleville Rehabilitation Center; 11 female alcohol, 10 male alcohol, 19 female drug and 19 male drug-dependent.

As indicated above, one major reason for selecting the three Centers was the diversity of their patient populations. For example, Eagleville subjects were younger than Philadelphia VA or Carrier patients (mean ages = 31,33,35 respectively). In addition, 88 and 73 per cent of Carrier and Eagleville patients (respectively) were white as compared with 42 percent of Philadelphia VA patients. Forty-two and 53 per cent of Philadelphia VA and Carrier patients (respectively) had been married, as compared with only 8 per cent of Eagleville patients. Carrier patients had an average monthly income from employment of $1300, 7% received welfare income, and fewer than 10% had been arrested. In contrast, Philadelphia VA subjects averaged $800 per month from employment, 39% received welfare income and 57% had been arrested. The average monthly income for Eagleville patients was less than $600, 44% received welfare income, and 72% had been arrested.

In the interest of brevity, only the data for the drug-dependent patients will be presented here.

Data Collection - Admission evaluations were based on data from the Addiction Severity Index (ASI). The ASI is a structured, 40-minute, clinical research interview designed to assess problem severity in seven areas commonly affected in substance abusers: medical condition, employment, drug use, alcohol use, illegal activity, family relations, and psychiatric condition.

Two types of measures result from the collected data in each problem area. First, the interviewer assimilates the objective and subjective data to produce a global, ten-point rating of the severity of each problem area.

The second type of measure available from the data in each ASI problem area is a mathematically derived composite score developed from interellated items within each ASI problem area and is similar to a factor score. An ASI copy with administration manual is available from the senior author.

Follow-Up Data - All follow-up evaluations were done through ASI interviews by an independent research technician, six months following treatment admission. Ninety-nine (84%) of the 118 drug-dependent patients were recontacted and received a follow-up interview.

STUDY I - EVALUATION OF TREATMENT EFFECTS

As one standard means of assessing treatment effectiveness, we compared a range of patient status measures from the ASI, at treatment admission and again at Six-month follow-up. Prior to performing these comparisons, we divided the Drug Dependent (N=99) sample into groups based upon treatment center. Admission to follow-up comparisons were then made using the paired t-test procedure. The results are presented in Table 1.

There were clear and expected differences in problem severity among the three patient subgroups at treatment admission, precluding meaningful between-center comparisons following treatment, although similar patterns of status change were seen among patients from the three Centers. For example, all groups showed significant ($p < .05$ or less) improvements in drug use, psychiatric symptomatology and family relations. Two of the three groups also showed significant improvements in employment, alcohol use and illegal involvement. Only the Carrier Clinic patients showed a significant reduction in medical problems over the six-month period.

The nature and extent of these changes are most clearly seen in the data for the combined drug-dependent sample (last two columns). For example, these patients reduced their days of opiate use by 80%, and showed reductions of 85% in stimulant use, 60% in depressant use and 57% in days of alcohol intoxication. Increases of 83% and 85% respectively were seen in the number of days employed and in the income earned, with corresponding decreases of 83% in days of criminal activity and 90% in illegal income.

STUDY II - PREDICTION OF OUTCOME RESULTS

Given the data from Study I indicating that patients treated in the three treatment Centers showed substantial and pervasive improvements, it was logical to ask what types of pre-treatment information might be most related to these improvements. This question was important to our research group since we had

previously performed a prediction-of-outcome study in an earlier sample of male veterans, using the ASI (McLellan et al., 1983). Thus, we were interested in whether the same types of pre-treatment information would again be predictive of outcome in a more diverse patient population and whether the ASI (which had not been used in this prognostic manner with patients other than male veterans) would be useful in this context. The subjects and methods of data collection were those previously described in Study I.

Methods of Data Analysis - We elected to use the stepwise multiple regression procedure from the BMDP statistical software package. This procedure sequentially tests categories of independent (predictor) variables to determine if they are significantly related to the criterion (outcome) variable, and then extracts that proportion of explained variation from the criterion variable prior to testing for further relationships among other predictor variables. In the present design, we first entered a number of patient demographic variables including age, race (0=black, 1=white), years of education, number of prior alcohol and drug abuse treatments, and marital status (single, married/cohabiting, divorced/separated); followed by our seven, ten-point ASI severity ratings at treatment admission; followed by the number of days spent in treatment and type of discharge from treatment (0=unfavorable, 1=favorable). Thus, the design enabled us to see whether our ASI measures of pre-treatment status were related to treatment outcome, after adjusting for the contribution of demographic differences among the patients.

Our prior work suggested that it would be important to evaluate several different aspects of patient outcome, and that different predictors were likely to be more important for different outcome measures. To overcome the problems in interpreting analyses derived from seven outcome measures we decided, a priori, to accept variables as significant predictors only if they reached a significant level of $p < .01$ on three or more of the seven outcome measures. We had used these procedures in our earlier work and they had the effect of eliminating spurious relationships, leaving the most robust and generalizable.

Results - Table 2 presents the results of the regression analyses for the drug-dependent patients in each treatment Center. The actual variables entered into the regression analyses and their average correlation (r) with all seven outcome measures are presented under each treatment center. Positive correlations indicate that higher scores on the predictor variable were related to poorer status (greater severity) on the outcome measures.

The data indicate considerable similarity in both the nature and extent of the predictor-criterion relationships for the drug-dependent samples from the three Centers. There were few important relationships between the demographic variables and the seven outcome measures. Fewer previous alcohol and drug treatments, and being married at the time of treatment admission, were somewhat related to better post-treatment status in Eagleville patients,

while no demographic variables were well related to outcome among Philadelphia drug abuse patients.

With regard to relationships between measures of pre-treatment problem status and follow-up outcome, the major predictors were the severity of psychiatric, employment, and legal problems for all three patient samples. In addition, the during-treatment measures of treatment length and type of discharge were also significantly and importantly related to patient status at follow-up. Collectively, the full range of predictors accounted for an average of 32 to 36 per cent of criterion variance across all seven follow-up measures.

DISCUSSION

Our first study attempted to measure the nature and extent of changes in drug-dependent patients treated at the Philadelphia VA Medical Center, the Carrier Clinic, and the Eagleville Hospital, using the Addiction Severity Index (ASI).

Results of the within-group comparisons indicated significant improvements in most of the seven criterion areas. The most significant improvements were shown in the target areas of alcohol and drug use, but highly significant improvements were also shown in the areas of employment, family and psychological status. The patients showed an 80% reduction in opiate use, a 60% reduction in depressant use, an 83% decrease in crime days, and an 85% increase in earned income. Fifty-two percent of the patients were drug free (excepting alcohol and marijuana) during the 30 days preceding follow-up. Thus, the evidence here and from other studies suggests that the major improvements following substance abuse treatment are in alcohol and drug use, but that there are several other areas that show moderate to major changes. Finally, the nature and extent of these improvements were quite similar across rather diverse treatments and patient populations, thus strengthening the generalizability of this conclusion.

In our second study, we attempted to use the admission data from the ASI to predict follow-up outcomes in samples from the three Centers. The results of the predictive analyses were quite similar among treatment centers, indicating relatively little predictive value for the majority of demographic variables. However, one of our aims was to determine the types of information that are potentially related to treatment outcome at the program level, since this is the point of maximum control and the site at which the various interventions are planned and carried out. Thus we conclude that at the program level, the typical kinds of demographic information available to the treatment staff are apparently not well related to post-treatment outcome, regardless of the type of treatment center or patient population.

The single best predictor of patients' overall status at follow-up was the ASI psychiatric severity rating at treatment admission. This ten-point, global estimate of the number and severity of a

patient's psychiatric symptoms has been operationally defined in prior work (McLellan et al., 1983) and has been used extensively as a predictor of treatment outcome in alcohol, drug, and psychiatric treatment studies. In addition, the data indicate that the severity of patients' employment and legal problems at treatment admission is also a robust and important indication of outcome following treatment. These results are identical to those reported in our prior work with male veterans; and very similar to those shown by Sells and Simpson (1976) in their national study of drug abuse treatment, and by DeLeon (1984) in his long-term follow-up work with drug abuse patients in a therapeutic community setting.

Given the results from these two studies and the accumulating literature which supports them, we conclude, first, that our original findings regarding the effectiveness of substance abuse treatments in a male veterans population were essentially replicated and do generalize to other treatments and populations. Second, we conclude that the usual demographic data and information regarding the amount, duration and intensity of a patient's substance abuse problem are often the least useful for planning treatment strategies, referring to an appropriate treatment modality, or predicting the overall outcome of treatment. Our findings here and from other studies indicate information regarding the pre-treatment psychiatric, employment and legal problems of these patients is likely to be the most useful in developing the most appropriate treatments for their alcohol and drug abuse problems. Regardless of whether they resulted directly from the years of chemical use, our clinical experience and a wealth of research data suggest that chemical abuse problems rarely occur without concomitant social, economic and/or psychiatric problems. Treatments that target the reduction and elimination of the alcohol and/or drug use without strongly addressing these ancillary problems leave the recovering patient at significant risk for relapse and progressive deterioration.

[1]From the Substance Abuse Treatment Unit of the Philadelphia VAMC, Philadelphia, PA 19104

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TABLE 1
ADMISSION TO SIX-MONTH FOLLOW-UP COMPARISONS IN
DRUG ABUSE PATIENTS

	PHILA VA N=44			CARRIER N=20			EAGLEVILLE N=35			ALL DRUG PATIENTS N=99		
	ADM		6-MO	ADM		6-MO	ADM		6-MO	ADM		6-MO
EMPLOYMENT COMPOSITE[1]	438	*	231	224		180	461	*	288	409	*	235
Days Working	5	*	11	12		13	4	*	10	6	*	11
Money Earned ($)	200	+	458	472		649	83	+	207	228	*	429
DRUG USE COMPOSITE	433	*	138	324	*	29	211	*	26	287	*	41
Days Opiates	26	*	3	7	*	1	4		2	10	*	2
Days Stimulants	8	*	2	8	*	1	4	+	1	7	*	1
Days Depressants	11		8	12	+	4	6	+	1	10	*	4
ALCOHOL USE COMPOSITE	195		157	357	*	101	127	*	65	207	*	91
Days Drinking	11		9	13	+	5	7	+	2	10	*	5
Days Intoxicated	7		5	10	+	3	4	+	1	7	+	3
LEGAL COMPOSITE	261	*	95	117	*	40	108		75	168	*	63
Crime Days	12	*	1	3		1	3		1	6	*	1
Illegal Income ($)	432	*	34	233	*	40	195	+	27	312	*	31
PSYCHIATRIC COMPOSITE	379	*	233	241	+	180	321	+	251	318	*	210
Days Psych. Probs.	15	+	7	9		5	13		10	13	+	7

[1]All criteria were measured during the 30 days prior to treatment admission and prior to six-month follow-up. Larger composite scores indicate worse status.

+ = $p < .05$ * = $p < .01$

TABLE 2
AVERAGE CORRELATIONS AMONG PREDICTORS AND OUTCOME CRITERIA IN 123
DRUG ABUSE PATIENTS FROM THREE CENTERS

DEMOGRAPHIC VARIABLES	CARRIER CLINIC (N=23)	EAGLEVILLE HOSPITAL (N=43)	PHILADELPHIA VAMC (N=57)
	(Average Correlations)		
Age in years	-.09	.14	-.11
Race (0=Black, 1=White)	-.11	-.12	-.14
Education in years	-.12	.06	.04
# Prior Alcohol & Drug Treatments	.18	.04	.07
Never Married (0=No, 1=Yes)	.06	-.18	.13
Divorced/Separated (0=No, 1=Yes)	-.12	.04	.10
Married/Cohabiting (0=No, 1=Yes)	-.21	.08	-.14
ASI SEVERITY RATINGS			
Medical	.16	.12	.17
Employment	.28*	.25*	.27*
Alcohol	.14	.17	.22*
Drug	.19	.18	.13
Legal	.22	.24*	.19*
Family/Social	.18	.27*	.20*
Psychiatric	.34*	.29*	.28*
WITHIN TREATMENT VARIABLES			
Days of Treatment	-.27*	-.34**	-.26*
Discharge (0=Favorable, 1=Unfavorable)	-.21	-.18	-.19
AVERAGE VARIANCE EXPLAINED (R^2)	36%	32%	36%

* = $p < .05$ ** = $p < .01$

[1]Multiple Regression analyses were run on seven outcome criteria. Higher criterion scores indicated worse status. Boxed values indicate that the predictor variable was significant ($p < .01$) on at least three of the seven outcome criteria (see text for discussion).

The 800-COCAINE Helpline: Survey of 500 Callers

Arnold M. Washton; Mark S. Gold; and A. Carter Pottash

ABSTRACT

Five hundred cocaine users who called the 800-COCAINE helpline received an extensive telephone interview to assess the nature, extent and consequences of their self-reported cocaine use. The data revealed a high incidence of dysfunctional cocaine use associated with numerous physical, psychological, and social problems. The typical caller was a white, middle-income male between 25 and 40 years old with no history of drug dependency or serious psychiatric problems. The findings are discussed with regard to the high abuse potential of cocaine and other factors that lead to problematic use and adverse effects.

INTRODUCTION

In response to the recent upsurge in cocaine abuse problems in the U.S., we established a nationwide telephone helpline, 800-COCAINE, to provide information, advice, and treatment referral. During the first year of the helpline's operation over 400,000 calls were received from across the U.S., sometimes at a rate of over 1,000 per day. Approximately 40% of calls are from cocaine users themselves: the remainder are from family members, friends or professionals seeking help or advice for someone with a cocaine problem.

We have now conducted a survey of 500 cocaine users who called the helpline and consented to an anonymous telephone interview. The purpose of the survey was to formulate a demographic profile of cocaine users and to obtain data on the nature, extent, and consequences of their cocaine use. With the exception of an earlier helpline survey (Washton and Tatarsky, 1984) and two recent studies of patients entering treatment (Helfrich et al., 1983; Siegal 1982) there have been virtually no large studies of problematic cocaine users. The relative absence of such studies tends to perpetuate the popular belief that cocaine is a

relatively harmless drug and that patterns of dysfunctional cocaine use are uncommon.

METHODS

An extensive questionnaire was administered to 500 randomly selected cocaine users who called 800-COCAINE during May through July 1983, and consented to an anonymous 30-40 minute telephone interview. In addition to demographic and drug use data, the questionnnaire included an extensive checklist of yes/no items concerning drug-related consequences on the user's health and psychosocial functioning. Most callers had learned of the help-line through media broadcasts. The largest proportion of calls (37%) came from the New York City metropolitan area. Other prime calling areas included California (17%) and Florida (12%).

RESULTS

Our random sample of 500 cocaine users was 67% male, 33% female, ages 22-59 years (X= 30 years); 85% were white and 15% were black or Hispanic. Mean level of education was 14.1 years. Forty percent had annual incomes over $25,000. Their preferred route of cocaine administration was: Intranasal (IN) 61%; freebase smoking (FB) 21%; and intravenous (IV) 18%. Estimates of weekly cocaine use ranged from 1-32 grams per week. Frequency of cocaine usage averaged 5.7 days per week; 48% used daily. At prices of $100-$125 per gram, the average amount of money spent per week on cocaine was over $637 and ranged from $100 to $3,150.

Sixty-one percent said they felt addicted to cocaine, 75% said they had control over cocaine use, and 83% said they were unable to refuse cocaine when it was available. Despite repeated attempts to stop cocaine use, 67% said they were unable to stay away from cocaine for as long as one month. Sixty-eight percent reported using tranquilizers, marijuana, alcohol, or heroin to reduce the stimulant effects of cocaine or to relieve the dysphoric "crash" when cocaine effects wore off.

Over 90% reported adverse physical, psychological, and social/financial consequences associated with their cocaine use. The incidence of specific consequences is shown in Table 1.

Table 1

INCIDENCE OF COCAINE-RELATED CONSEQUENCES
(N=500)

Physical Effects	N	Percent
sleep problems	410	82%
chronic fatigue	380	72%
severe headaches	300	60%
nasal sores, bleeding	291	58%

(Table 1 cont.)

chronic cough, sore throat	228	46%
nausea, vomiting	193	39%
seizure, loss of consciousness	70	14%

Physical Effects	N	Percent
depression	415	83%
anxiety	416	85%
irritability	408	82%
apathy, laziness	328	66%
paranoia	326	65%
difficulty concentrating	323	65%
memory problems	287	57%
sexual disinterest	265	53%
panic attacks	248	50%

Additional drug-related consequences included loss of: job (25%), spouse (25%), friends (51%), and all monetary resources (42%). Automobile accidents (11%), fighting and violent arguments (59%), and cocaine-related suicide attempts (9%) were also reported. A substantial number of callers reported stealing from work, family, or friends (20%) and dealing cocaine (39%) in order to support their expensive cocaine habit.

DISCUSSION

This study provides self-reported evidence of adverse physical and psychosocial consequences of cocaine use in a sample of 500 callers to the helpline. Our findings expand an accumulating body of data that points to the risks and dangers of cocaine use (Wetli and Wright, 1979; Gold, 1984). A previous helpline survey of 55 cocaine users (Washton and Tatrasky, 1984) and a recent study of 136 cocaine abusers who entered treatment (Helfrich et al., 1982) reported numerous physical, psychological, and social problems associated with chronic cocaine abuse. In conjunction with these earlier reports our study highlights the fact that intranasal users are not exempt from developing a strong dependence on cocaine or from suffering adverse effects on their health and functioning. It is now evident that dysfunctional cocaine use can and does occur not only in freebase and i.v. users, but in intranasal users as well (Washton et al., 1983; Stone et al., 1984).

Helpline surveys and studies of treatment populations present a somewhat skewed picture that is not necessarily representative of all users. One would expect that dysfunctional patterns of drug use and serious adverse effects would be more prevalent among a sample of self-defined problematic users than among a true cross-section of all users. For example, in a study of 85 self-defined "social-recreational" cocaine users, Siegel (1977) reported that occasional intranasal use had resulted in remarkably few problems demanding clinical attention. While it is undoubtedly true that some users exhibit controlled usage patterns and no serious

adverse effects, one must be careful not to conclude from such observations that even occasional cocaine use is harmless. Occasional use can pose subtle and accumulating risks that are often inadequately recognized. Many "recreational" cocaine users acquire a growing dependence on the drug without fully realizing it. The weekend "snorter" gets accustomed to using cocaine in order to insure a good time and eventually begins to feel incapable of being happy, sharp, sexy, confident, or sociable without cocaine. The seductive and compelling effects of cocaine encourage the occasional user to want more of the exalted feeling and in more varied situations. This may lead to increases in both the dosage and frequency of use and in some cases to a switch from snorting to more potent forms of administration, such as freebasing. Due to progressive tolerance, continued use may lead to a diminished euphoric response, thereby ensnaring the occasional user into a vicious cycle of intensifying use in a futile attempt to recapture the fleeting cocaine "high". With chronic escalating use, not only does the euphoria diminish, but the rebound dysphoric "crash" also intensifies and further drives continued and escalated use. The weekend user will typically feel lethargic, irritable, depressed and generally "hung over" on Monday mornings leading to lateness, absenteeism, or reduced effectiveness at work. Occasional users who have become increasingly conditioned to cocaine's effects may sharply escalate their use if they experience a life crisis or a particularly stressful period because they have come to associate the drug with "feeling better", i.e., stress relief. Cocaine seems to have a subtle ability to delude the users into thinking that their intake of the drug is not problematic. Legal consequences for buying or possessing cocaine with possible ruination of job or career are potential risks even for the occasional user. Many users resort to dealing cocaine in order to offset the high cost of their own cocaine habit. Legal penalties for cocaine dealing can be extremely severe. In light of these numerous but often unanticipated consequences, it is difficult to conclude that occasional cocaine use is completely harmless.

Consistent with previous studies (Washton and Tatarsky, 1984; Helfrich et al., 1982) intranasal users accounted for over half of the present sample, indicating that "snorting" cocaine continues to be the most popular method of self-administration. However, smoking cocaine freebase seems to be steadily gaining in popularity despite its increased risks (Siegel, 1982). Freebase is a more volatile form of cocaine that readily lends itself to being smoked because it has a lower melting point than the street-bought cocaine hydrochloride. Through a simple chemical process street cocaine is "freed' from its hydrochloride salt to yield the freebase which is typically smoked in a glass waterpipe. As compared to intranasal cocaine, freebase smoking results in a more rapid and direct absorption of the drug into the bloodstream, a quicker and more intense euphoric reaction, and increases both the abuse potential and risk of toxic reactions. With freebase smoking there is not only a more intense euphoria but also a more

intense rebound dysphoria that tends to engender compulsive patterns of use. The sharp rise in cocaine plasma levels and the intense euphoric "rush" with freebase smoking is nearly identical to that with intravenous injection (Perez-Reyes et al., 1982). Cocaine users who might never resort to i.v. use of the drug are now turning to freebase smoking as a means of achieving the same type of effect but without the social stigma of using needles. Intranasal users who have switched to freebasing report that it leads to dramatic increase in cocaine use characterized by exaggerated binges, a more extreme obsession with the drug, and a marked qualitative and quantitative difference in the euphoric experience. The subjective effects of freebasing are described as being more sexual, more alluring, more detached from reality, and more blissful. The widespread distribution and sales of freebasing pipes and other cocaine-smoking paraphernalia (Siegel, 1982) reflect the growing acceptance of this practice among users.

Cocaine use appears to promote the use and abuse of other drugs that are usually taken to offset the negative side effects of chronic cocaine abuse. Seventy-eight percent of the present sample reported use of alcohol and other CNS depressants to relieve the dysphoria "crash" or to reduce the unpleasant stimulant effects of cocaine. Alcohol is by far the most popular substance used for this purpose. Because alcohol or other drugs are taken by the cocaine user not to get "high" but to self-medicate for cocaine side effects, the user is often unaware of a growing dependency on these substances and may eventually acquire a second addiction. There is also an increased risk of overdose reactions to drugs used to counteract cocaine. The strong intoxicating effects of CNS depressants which would normally signal the potential for the stimulant effects of cocaine wear off. Similarly, auto accidents on cocaine are often due to the combined use of cocaine and alcohol. The intoxicating effects of the alcohol may not be felt when the cocaine user first gets behind the wheel of the car, but may subsequently cause a blackout when the cocaine wears off and the alcohol effects come on with full force. Fifty-seven subjects in the present study (11%) reported a cocaine-related automobile accident. In most of these cases it was due to combined use of cocaine and alcohol. The role of cocaine use in traffic accidents and fatalities is probably underestimated to a large extent because persons stopped for driving while intoxicated are rarely tested for the presence of cocaine in blood or urine.

The 800-COCAINE helpline has afforded a unique opportunity to study a large population of cocaine users that might not otherwise be accessible for scientific or public analysis. The large and steady volume of calls to the helpline from numerous geographical areas across the U.S. suggests that adverse effects of cocaine use are severe enough to cause large numbers of users to seek assistance. Over 50% of cocaine users calling the helpline request a treatment referral, but it is estimated that fewer than 20% of these referred callers actually enter treatment. In many cases,

the user's persistent denial of the full extent and severity of their problem as well as their need for outside help, pose major obstacles to entering treatment. Those who enter treatment usually do so as a result of an immediate crisis situation, such as the threat of job loss, marital separation, financial ruin, legal trouble, or serious disruption to their health and functioning. The 800-COCAINE helpline has served to decrease some of the obstacles to seeking help. It guarantees the anonymity of the caller and provides a toll-free telephone number that is easy to remember and has intuitive appeal. The helpline may encourage some users to seek treatment before a serious crisis arises, but to date we have no hard evidence to indicate that this is actually occurring. Nonetheless, the helpline experience seems to have helped to increase public awareness of cocaine problems and to counter the long-standing myth that the drug is harmless.

With the increasing prevalence of cocaine use and intensified usage patterns, a more complete picture of the potential consequences has begun to emerge. Cocaine is an insidious drug with a long-standing image of being harmless and non-addictive. Recent experience suggests that if social sanctions or medical research failed to caution against the potential dangers, the already widespread occurrence of dysfunctional cocaine use would continue to rise.

FOOTNOTE

1. A longer version of this paper appeared in Psychiatric Annals, 14: 190-197, 1984, and is reprinted with permission of the publisher Charles B. Slack, Inc., Thoroughfare, N.J.

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The Effect of Questionnaire Design on Reported Prevalence of Psychoactive Medication

Linda B. Cottler and Lee N. Robins

INTRODUCTION

Valid estimates of the amount of medical and non-medical drug use in the general population are necessary to understand the extent of drug-attributable illness. Estimates of psychoactive medication use can be obtained through methods such as surveillance of patient medical records, or of pharmacy prescriptions. Underestimates may result from surveillance of patient records because physicians may not always document in the record the prescriptions they write, and do not always obtain from patients complete medication histories of prescribed and over-the-counter medications. Pharmacists' records, on the other hand, may overestimate prescription use, since the fact that a prescription has been filled by a pharmacist does not necessarily indicate its utilization by the patient.

Estimates can also be obtained from retrospective interview studies, but efforts must be made to control selective and faulty recall. Parry et al. (1970-71) demonstrated that good questionnaire design could appreciably improve a respondent's recall of psychoactive drug use. In this paper, we evaluate the effect of questionnaire design on reported prevalence of prescribed and non-prescribed psychotherapeutic medication use. In addition, we describe the reported indications for use of these medications.

METHODS

The data for this paper were taken from the first wave of the St. Louis NIMH Epidemiologic Catchment Area (ECA) study, conducted from April 1981 to March 1982. The study, aimed at determining incidence and prevalence rates of psychiatric disorders in the general population, used the NIMH Diagnostic Interview Schedule(DIS) and Health Services Questionnaire(HSQ) (Eaton et al. 1981). The DIS is a structured interview which obtains information necessary to make over 30 of the diagnoses defined in the Diagnostic and Statistical Manual, 3rd Edition (American Psychiatric Association

1980). In addition to health services utilization, the HSQ elicits information on demographic characteristics and medication use. Stratified cluster sampling techniques were used to select 3778 households for participation from three Mental Health Catchment Areas in Metropolitan St. Louis. These areas were chosen because together their 1970 population resembled the demographic composition of the nation as a whole. After a household member completed a screening interview which enumerated household residents over age 18, one person per household was randomly designated to participate in the study; replacement for any reason was not allowed. The interviewed sample was 3004 persons, representing an 80% response rate. The interview took approximately 90 minutes and was administered by professional interviewers who had undergone intensive training. Before beginning the interview, respondents were told that their interview was completely confidential, and could not be linked to them individually. The medication utilization section within the HSQ was introduced by a statement explaining that the respondent would be asked about medications taken in the past six months, whether prescribed, over-the-counter, or obtained from friends, relatives or neighbors. The questions were asked in the following sequence:

1. "During the last six months, that is, since (DATE 6 MONTHS PRIOR) have you taken any medications to help you calm down or keep you from getting nervous or upset?"
2. ".....to raise your spirits, or to help you feel less moody or depressed?"
3. ".....to help you get to sleep or stay asleep?"
4. ".....help you with a drug or alcohol problem?"
5. ".....for a nervous stomach?"
6. ".....to give you more energy or to cut down on your appetite?"

When the response was "yes", the interviewer ascertained which medications were used at least three times in the last six months, and how they were obtained.

The questions just described are the indication-specific questions. Although they are not exhaustive, it was felt they included the most common reasons for taking psychoactive medications. These questions were followed by six medication-specific questions:

> "In the past six months, that is, since (DATE SIX MONTHS PRIOR) have you taken any (Elavil/Valium/Librium/Dalmane/Thorazine/Mellaril) for any emotional problems or problems with drugs or alcohol?"

Brand names were used because we felt respondents would be familiar with them. However, all drugs were coded by generic name so that similar drugs mentioned in the indication-specific questions would be counted equally. The source from which the medication was obtained was elicited for these drugs also, provided they were used at least three times in the last six months.

RESULTS

Table 1 shows six-month prevalence rates for the six drugs asked about by name. The rates are given for the proportion of the

sample using each drug and whether its use was elicited by the indication question, or by the medication question after being missed by the indication question. Valium was the psychoactive drug used most among the six inquired about, followed by Librium, Elavil, and Dalmane. Thorazine and Mellaril were infrequently used (by less than 0.5%). Had only the indication-specific questions been asked, the rate of Valium use would have been 5.06%. The medication-specific question accounted for an additional 65 users, or 2.19%, which raised the estimated prevalence of Valium use to 7.25%.

TABLE 1
Six-month prevalence rates of psychoactive drug use by question asked (N=2962)

	Indication-specific		Medication-specific		Total	
	f	%	f	%	f	%
Valium	150	5.06	65	2.19	215	7.25
Librium	54	1.83	23	.78	77	2.61
Elavil	33	1.11	12	.41	45	1.52
Dalmane	26	.88	9	.30	35	1.18
Thorazine	7	.24	4	.14	11	.38
Mellaril	7	.24	4	.14	11	.38

(Ns varied for each drug--4 persons had missing information.)

As shown in Table 2, by asking the additional medication-specific questions following the indication questions, prevalence rates of psychoactive drug use increased between 35 and 57%. Reporting of Thorazine and Mellaril, drugs used infrequently in our sample, was especially augmented by the name-specific questions. Estimated prevalence was increased 43% for both Valium and Librium. On the average, the reported prevalence increased 42% for these six drugs. Responses to the medication-specific questions accounted for between 26 and 36% of each drug's total use, and on the average, accounted for 30% of the prevalence rate for these six drugs.

TABLE 2
Increase in estimated prevalence of psychoactive drug use attributed to asking the medication-specific questions

	% increase in prevalence	% of total
Thorazine	57%	36%
Mellaril	57	36
Valium	43	30
Librium	43	30
Elavil	36	27
Dalmane	35	26
Mean	42	30

The responses to the indication-specific questions show that respondents are able to differentiate the reasons for their drug taking (Table 3). For example, of the 432 reports of use of some drug "to calm down", Valium was the most widely used of these six drugs; it accounted for 32% of the use for this indication. Librium was the next most prevalent. When respondents were asked which medications were taken to help them feel less moody, Elavil and Valium were the most commonly used of the six, accounting for 13% and 10% respectively of all drugs used for this problem. Valium, Dalmane, and Elavil were the drugs most often used to treat sleep problems; Librium was the only one of the six reported to be used for a drug or alcohol problem. These six medications were rarely used to treat a nervous stomach. No one reported using one of these drugs "to give more energy or decrease appetite". These six medications accounted for more than half (53%) of all medications used to calm down, 30% of medications taken to treat mood problems, and one-third of the medications taken to induce sleep.

TABLE 3
Selected psychoactive drugs
among all drugs used for a specific indication

	Calm down	Mood	Sleep	Drug/Alc problem	Nervous stomach	Energy/ appetite
Elavil	6%	13%	8%	0	*	0
Valium	32	10	12	0	*	0
Librium	11	*	3	11	1	0
Dalmane	*	3	9	0	0	0
Thorazine	2	2	*	0	0	0
Mellaril	2	2	2	0	*	0
% accounted for by these drugs	53	30	34	11	3	0
No. of drug uses	432	120	258	18	362	284

* less than 1%

Each drug was analyzed by the indications given for its use, with every drug mention being counted separately. As shown in Table 4, Elavil was mentioned 75 times in response to the indication questions. Over a third of its use was reported for the indication "to calm down", and over a quarter of its use was reported for sleep. Only 19% of its use was as an anti-depressant. Just over half of the use of Valium and Librium was consistent with their anxiolytic properties (i.e., to calm down). For Dalmane, two-thirds of its use was appropriately to induce sleep; yet some persons

reported its use as a tranquilizer or as an anti-depressant. Use patterns of Thorazine resembled those of Valium: the most common reason for use was to calm down. Mellaril was used more like Elavil, to calm down and to induce sleep predominantly. It is noteworthy that these indication questions accounted for as much of the use of major as minor tranquilizers, even though "suppression of psychotic symptoms " was not one of the indications inquired about. The reasons for use of from 16 to 26% of each of these drugs is not known, because their use was reported only after the name-specific questions were asked.

The groups whose reporting was increased most by the addition of the medication-specific questions are shown in Table 5. The young (25-44 year olds), blacks, males, and persons with at least eight years of education were the groups most likely to increase recall of their medication use in response to the drug-specific questions. Exceptions to this were found for Elavil, where reported use was most enhanced for the 45-64 year olds, and for Valium, where recall by both the oldest group and the young group was strikingly enhanced by the medication question. There was no difference in the degree of enhancement of the reporting of Librium by race or sex.

TABLE 4
Reasons given for psychoactive drug use*

	Elavil	Valium	Librium	Dalmane	Thorazine	Mellaril
To calm down	35%	56%	54%	6%	47%	39%
To help mood	19	5	2	8	13	11
To get to sleep	27	12	10	62	7	22
For a drug/ alcohol problem	0	0	2	0	0	0
For a nervous stomach	3	1	6	0	7	6
No indication (Med-specific)	16	26	26	24	26	22
Total mentions of use (N)	(75)	(250)	(89)	(37)	(15)	(18)
%	100	100	100	100	100	100

* each of multiple indications per respondent counted

TABLE 5
Groups whose reporting was increased most by adding medication-specific questions

	Elavil	Valium	Librium	Dalmane
Age	45-64	25-44 and 65+	25-44	25-44
Race	blacks	blacks	no diff.	blacks
Sex	males	males	no diff.	females
Education	>8 yrs.	>8 yrs.	>8 yrs.	>8 yrs.

While most of these drugs were obtained by physicians' prescriptions, some of each, except Mellaril, were obtained from friends, relatives, or on the street. (We do not know if the original owner got them by prescription.) We assessed whether or not the additional name-specific questions changed our estimate of the proportions obtained through non-medical channels (Table 6). In the case of each drug, these questions did elicit a higher proportion of non-prescribed drug use than was obtained with the indication questions. The proportion of use which was not by personal prescription would have been underestimated if the medication-specific questions had not been asked.

TABLE 6
Percent non-prescribed of all reported drug use, by indication or medication question

	Indication-specific	Medication-specific
Elavil	3%	10%
Valium	12%	25%
Librium	12%	24%
Dalmane	0	29%
Thorazine	0	25%
Mellaril	0	0

DISCUSSION

For six common psychoactive medications, prevalence rate estimates were increased an average of 42% by following indication-specific questions with name-specific questions. The drug-specific questions accounted for 30% of the prevalence rates on the average. Increased recall, as a result of the drug-specific question, was especially great for blacks, males, those 24-44 years old, and for infrequently used drugs such as Thorazine and Mellaril.

Finding a substantial average percent increase in prevalence for these six drugs suggests that estimates of use of other psychoactive drugs we did not inquire about by name probably should be approximately doubled.

These findings corroborate those of Parry et al.(1970-71) that intensive questioning appreciably increases reporting of psychoactive drug use, especially for males and persons with more than an eighth grade education. In a previously published paper (Cottler and Robins 1983) we reported that women's use of psychoactive drugs was twice that of men's. This ratio would have been even greater if the name-specific questions had been eliminated.

A considerable increase in recall of medication utilization can be expected from a simple addition of questions. Thus, careful questionnaire design can minimize one of the disadvantages that retrospective interview studies have long borne.

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Young Adult Marijuana Use in Relation to Antecedent Misbehaviors

James C. Anthony

An estimated 15 to 20 percent of Americans aged 18-34 are recent marijuana smokers (derived from Fishburne et al., 1980). The average prevalence of daily and near-daily marijuana use is closer to 5 or 10 percent, with male rates higher than female rates. A profile of toxicity is not complete, but this prevalence of daily and near-daily exposure to marijuana warrants increased attention because of the potential public health hazard (Institute of Medicine 1982).

Aggressiveness in early childhood and other conduct problems or misbehaviors have been associated with later high levels of involvement in marijuana smoking, particularly among males (Robins 1980; Kellam et al., 1983). These early antecedents may be modifiable factors that influence either the risk of becoming a daily smoker or the duration of of daily smoking, or both. If so, they have potential importance in efforts to prevent and control the drug-using behavior, and to reduce the degree of drug hazard.

The casual importance and modifiability of early antecedents like childhood aggression can be thoroughly tested only with experiments and quasi-experiments, including preventive trials in community settings. This paper represents and intermediate step in that direction, with a more modest aim: to test the strength and nature of association between young adults' recent level antecedent misbehaviors such as truancy and stealing. Males and females are examined separately because previous investigators have found sex differences in the developmental paths toward drug use (Ensminger et al., 1982).

METHODS

In 1981, special trained lay interviewers completed 60-90 minute interviews with 3481 adults aged 18 and over who had been sampled for the NIMH Epidemiologic Catchment Area (ECA) household survey in eastern Baltimore. The sample was drawn to be representative

of the area's adult household population. The survey response rate was 78%. The interview consisted of many standardized socio-demographic and health-related measures, including the NIMH Diagnostic Interview Schedule of DIS (Robins et al., 1981).

The DIS information is based mainly on what subjects report about themselves. In this study DIS self-report data have been used to provide measures of: (1) misbehavior before age 18; (2) age at first non-medical drug use: and (4) DSM-III Anti-Social Personality Disorder.

Subjects' responses to 10 DIS items on misbehavior were tallied to produce an index of misbehavior before age 18. The DIS items covered school misbehavior, expulsion or suspension, hookey, fighting in and out of school, running away from home, telling lies, stealing, intentional damage to property, and juvenile arrests. The DIS items on school performance and early use of alcohol or street drugs were excluded from the tally. Reliability of the index, estimated by Cronbach's alpha, was 0.72

For this study, the index was dichotomized with 0-2 misbehaviors forming one group, and 3-10 forming the other. This cutting point was chosen after examining the marginal distributions of the index for males and females, prior to cross-classification with drug variables.

The interview included standardized questions on recent non-medical drug use. Every subject who reported use of marijuana or other cannabis products was asked, "During the past month, on about how many different days did you take marijuana, hashish, [etc.] for a non-medical reason?" The response provided the measure of marijuana use for this paper.

The reported sample sizes indicated the number of subjects actually interviewed. The proportions have been weighted to account for survey sampling and non-participation factors. A more complete description of the weights and other methods of the survey is published elsewhere (Eaton and Kessler, in press).

The degree of association between young adults' recent marijuana use and antecedent misbehaviors before age 18 is indexed by tau, which may be viewed as a qualitative analogue to the coefficient of determination for continuous data [R-squared] (Bishop et al., 1975). The test statistic, U-squared, is presented to test the hypothesis of no association. It is based upon the weighted proportions and the effective sample size for each table (not the weighted number of persons).

RESULTS

Males. 495 males aged 18-34 completed interviews for this study. Their responses to the non-medical drug use questions indicated recent marijuana use by an estimated 34 percent of

18-34 year old males living in eastern Baltimore households in 1981. An estimated 13 percent were daily or near-daily users (based on reported 14-31 days of use during the month prior to interview).

Table 1 indicates that among males there was an association between recent marijuana use and the antecedent misbehaviors. As a group, males with no recent use of marijuana were least likely to have a history of three or more antecedent misbehaviors. Males with 14-31 recent days of use were most likely to have a history of the misbehaviors. There was a non-significant trend across the three levels of recent marijuana use. The p-value indicates the statistical significance of the association. Tau indicates an estimated 10 percent common variance.

This association held up through a series of analyses to control for potential confounding variables and special features of the sample. That is, the association persisted among males with no history of DIS-ascertained Anti-Social Personality Disorder; among males with no history of DIS-ascertained Abuse and/or Dependence involving opioids, cocaine, sedative-hypnotics, or hallucinogens; and among males whose non-medical drug use did not begin until after 17. The association also persisted when the analysis was restricted also persisted when the analysis was restricted to the 294 young white males in the sample.

TABLE 1.

History of antecedent misbehavior is associated with recent marijuana use among young adults (Eastern Baltimore ECA Survey, 1981)

	Days of Recent Marijuana Use			
Young Adults, 18-34	NONE	1-3	4-13	14-31
Number of males	331	40	58	66
Proportion with history or prior misbehavior	31 %	68 %	52 %	71 %
U-squared = 51 (df = 3) p less than 0.001				
Number of females	624	64	34	59
Percent with history of prior misbehavior	17 %	36 %	38 %	65 %
U-squared = 76 (df = 3) p less than 0.001				

Females. 781 females aged 18-34 completed interviews for the study. Their responses to the non-medical drug use questions indicated recent marijuana use by an estimated 19.0 percent of 18-34 year old females living in eastern Baltimore households in 1981. An estimated 7 percent were daily or near-daily users.

Table 1 shows that for females as for males there was an association between recent marijuana use and antecedent misbehavior before age 18. An estimated 17 percent of females with no recent use had a history of three or more misbehaviors, compared with 65 percent of females with 14-31 recent days of use. The data on males indicated no trend across the three levels of recent marijuana use, whereas the data on females suggest stepwise increments in the percentages relative to the number of recent days of use. The p-value indicates statistical significance of the association. The estimated tau indicates 10 percent common variance.

The observed association and stepwise trend persisted among young females with no history of Anti-Social Personality Disorder; among those with no history of Abuse and/or Dependence involving opioids, cocaine, sedative-hypnotics, or hallucinogens; and among

the 362 young white females in the sample. When the analysis was restricted to young women with no reported history of non-medical drug use prior to age 18, the association persisted but the stepwise trend disappeared.

DISCUSSION

Based upon standard survey techniques with a sample that was constructed to be representative of the adult household residents of a defined area, these results provide additional evidence of an association between the marijuana use of young males 18-34 years old and antecedent misbehaviors before age 18. The results indicate that an association of similar strength exists for young women as well -- at least in eastern Baltimore of 1981.

The association persisted when the analysis included control over histories of Anti-Social Personality Disorder, Abuse and/or Dependence involving drugs other than marijuana, and onset of non-medical drug use prior to age 18. Thus, the association is not solely a function of these factors. In addition, the association was found for both white males and white females, and cannot be explained solely in terms of white-nonwhite difference.

There is an alternative explanation for the association. Namely, subjects who report marijuana use may provide more complete accounts of their misbehaviors during childhood and adolescence. Others have suggested that this may not be a major problem in studies of this type (Robins 1974). No test of this alternative explanation was possible here.

It was somewhat surprising to find that a history of antecedent misbehaviors did not discriminate between levels of recent marijuana use among the young males, even when cases of Anti-Social Personality Disorder were taken out of the analysis. It was also surprising to find the contrary for the young females. These were unanticipated findings that require for developmental paths toward drug use. Preventive intervention studies may find that both low and high levels or marijuana involvement are affected when early misbehaviors are modified among males, with only high levels affected among females.

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A Prospective Twelve-Year Follow-up of Alcoholic Women: A Prognostic Scale for Long-Term Outcome

Elizabeth M. Smith and C. Robert Cloninger

The clinical evaluation of prognosis in alcoholic women has become an important research priority due to the recent increase in the prevalence of alcohol abuse by women. The search for predictors of outcome in alcoholism has generated extensive literature, but few data are available about alcoholic women. The purpose of the present study was to examine the long-term course of alcoholism in women who were systematically interviewed and diagnosed according to rigorous criteria at index and to identify pre-treatment characteristics associated with various outcomes twelve years after hospitalization. In this paper we describe the first multivariate scale to predict prognosis in alcoholic women.

SUBJECTS AND METHODS

Subjects: The subjects were 103 women who were consecutive alcohol admissions to two psychiatric hospitals in the St. Louis area, one public and one private, during 1967-68. They were collected as part of a clinical and family study of alcoholism. (Schuckit et al., 1969; Winokur et al., 1971).

The mean age at admission was 44 years, with a range from 18 to 67 years. The majority (76%) were white and most (65%) were drawn from the private hospital. They were evenly divided between lower (public hospital and ward patients) and middle to upper socioeconomic status (private patients). The mean number of years of problem drinking prior to admission was nine years, with a range from one to 38 years. Seventy-five percent of subjects had previously been hospitalized for alcohol problems.

During the hospitalization, each subject was given a structured psychiatric interview which emphasized family history of psychiatric illness, chronology of development of psychiatric symptoms as well as the history of alcohol use, including the extent and time sequence of problem drinking, any periods of abstinence, and consequences of alcohol abuse.

Diagnostic Criteria: Although the original study was conducted before all of the operational criteria were developed, the diagnostic criteria used are essentially the same as those which have become known as the Feighner criteria (Feighner et al., 1972).

When a patient developed symptoms of another disorder prior to the onset of a syndrome of alcohol abuse, that disorder was considered primary. If the symptoms developed during or after a period of alcohol abuse, the alcoholism was considered primary.

The subjects fell into three major diagnostic categories based on the time course of the development of symptoms. The majority (59%) were primary alcoholics and about one-half of this group had a diagnosis of secondary depression. Twenty-five percent of subjects received a diagnosis of primary affective disorder (unipolar depression) and 7% were diagnosed as antisocial personality. The remaining 9% received various other primary diagnoses, including schizophrenia, hysteria, drug addiction, and obsessional neurosis with secondary alcoholism.

Follow-up: We were able to follow up 90% of the subjects. Three could not be located and eight refused to be interviewed, reducing the sample from 103 to 92. Follow-up interviews were conducted during 1979-80, approximately twelve years after hospitalization. A structured psychiatric interview, the NIMH Diagnostic Interview Schedule (Robins et al., 1981) was utilized with expanded sections on alcohol and drug use, health, work, and marital history. Detailed information was obtained on the subject's course since discharge from the hospital including quantity and frequency of alcohol use, any periods of abstinence or periods of uncomplicated social drinking, any treatment for alcohol problems, and any consequences of alcohol abuse including legal, marital, job or health problems.

If the subject was dead or could not be interviewed, information was obtained from the closest available relative using the same structured interview. Death certificates were obtained for all subjects who died and medical and psychiatric records obtained for those who had been hospitalized during the follow-up period.

Outcome: Subjects were classified into four outcome groups based on the length of time during the follow-up period spent free of alcohol-related life problems, including both social adjustment and medical symptoms. Utilizing methods similar to those of Schuckit and Winokur (1972), we recorded the number of months or years during the follow-up period when the subject was able to work, care for her family or herself, and perform other social roles without impairment due to alcohol. During a period of heavy drinking all problems that occurred were considered to be alcohol-related.

This outcome scheme avoids the pitfalls of using abstinence as

the sole outcome criterion, which in effect excludes women who return to uncomplicated social drinking. It also utilized a longitudinal rather than cross-sectional approach in classifying the subjects' behavior and functioning.

The four outcome categories are: Incapacitated - subjects had an unremitting course with less than one year spent free of alcohol problems. The majority of subjects in this group died as a result of alcohol abuse. Poor - those who had at least one full year but less than three consecutive years free of alcohol problems. Good - those who had at least one period of three consecutive years free of alcohol problems. This group contained a substantial minority of episodic drinkers who had a variable course with periodic relapses. Excellent - those who had fairly continuous remission from alcohol problems with good social functioning for the major part of the follow-up period.

Predictor Variables: The number and type of predictor variables were limited to items from the first interview and their selection was based on prior research findings. Index information was available in four areas: social and demographic characteristics; familial and marital history; psychiatric diagnosis; and alcohol and drug history and complications.

Statistical Analysis. Because of the small numbers, the poor and incapacitated groups were combined, as were the good and excellent groups, yielding two outcome groups: Poor (n=47) and Good (n=45) outcome. Discriminant function analysis was used to identify the index variables that distinguished good outcome women from those with poor outcomes at twelve year follow-up. The 32 index variables were entered in the discriminant function analysis with outcome as the criterion variable. The stepwise solution method was used to select variables that minimize Wilk's Lambda (F for inclusion or deletion, 1.0; tolerance level, .001). Discriminant analysis was also used to classify good and poor outcome subjects.

As a test of the replicability of the results obtained from the original analysis we performed a series of five discriminant analyses, each time removing a random sample of ten subjects from the two outcome groups.

RESULTS

Forty-nine percent of the subjects had good long-term outcomes with an average of 7.9 years free of alcohol-related problems, while 51% had poor outcomes with less than one year (mean = eight months) free of problems. The mortality rate for the located sample was 31%. With few exceptions, subjects who died had continued to abuse alcohol and most experienced a fairly steady downhill course with the majority of deaths the result of alcohol-related causes including cirrhosis, accidents, and suicide.

Significant Predictors of Long-Term Outcome. We turn now to the results of the discriminant analysis of the 32 index variables. Table 1 shows the fifteen significant variables in their order of entry into the model.

TABLE 1 VARIABLES AT ADMISSION THAT DISTINGUISHED GOOD VERSUS POOR OUTCOME AT 12-YEAR FOLLOW-UP*

Predictor Variables	Value On Discriminant Function†	Mean Value/ Percentage of Each Outcome Group	
		GOOD (N=45)	POOR (N=47)
History of Delirium Tremens (0,1)	+.22	7%	32%
Unemployed (0,1)	+.52	5%	26%
Admission for Loss of Control (0,1)	+.48	29%	55%
Antisocial Personality (0,1)	+.61	0%	13%
Psychiatrically Ill Mother (0,1)	+.44	29%	37%
Problem Husband (0,1)	-.29	36%	28%
Early Onset (0,1)	+.51	38%	56%
Years of Education (years completed)	-.51	11.7	11.4
Low Socioeconomic Status (0,1)	+.59	40%	60%
Never Abstained (0,1)	+.28	36%	41%
Primary Diagnosis of Alcoholism (0,1)	+.39	60%	64%
Age at Admission (years)	-.64	41.9	41.1
Duration of Alcoholism (years)	+.51	7.9	10.1
Married and Living with Husband (0,1)	-.22	56%	35%
Blackouts (0,1)	+.20	55%	77%

* The variables were found by discriminant analysis ($P<.0001$) and are shown in the order in which they entered. Coding of variables is indicated in parentheses. The group means of variables that are present (1) or absent (0) are the proportion who have that factor and are listed as percentages.

† High positive values on the discriminant function distinguish women with poor outcomes from the others. The tabulated values are standardized canonical discriminant coefficients that indicate the relative weight and direction of influence of each variable.

These variables accounted for 44% of the variance and correctly classified 83% of the subjects according to long-term outcome. Subjects in the two outcome groups were classified equally well, with 84% of those in the good outcome group and 81% in the poor outcome group correctly classified.

Since many of these variables were highly correlated, we wanted to identify a reduced predictive model with fewer variables. Therefore, we selected the seven variables that were individually most highly correlated with outcome (see Table 2).

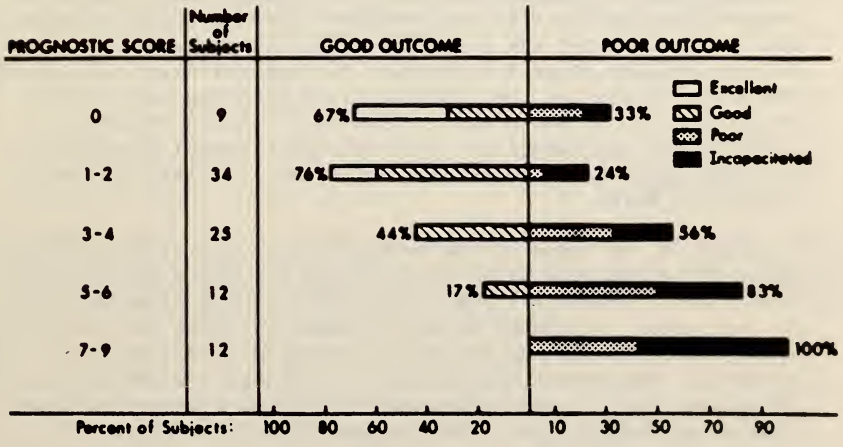
TABLE 2 A REDUCED PROGNOSTIC MODEL IN WHICH ALL 7 VARIABLES ARE INDIVIDUALLY ASSOCIATED WITH OUTCOME

Prognostic Variables	Unstandardized Discriminant Value	Individual Strength of Association χ^2	P
Major Predictors			
Delirium Tremens	1.19	9.31	<.002
Unemployed	1.36	7.92	<.005
Antisocial Personality	1.57	6.15	<.01
Admission for Loss of Control	0.99	6.58	<.01
Minor Predictors			
Early Onset of Alcoholism	0.54	2.84	<.09
Unmarried/Not Living with Husband	0.20	4.31	<.04
Low Socioeconomic Status	0.13	3.52	<.06

The discriminant function analysis using these seven variables correctly classified 76% of the subjects. This reduced model provided classification results which were almost as good overall as the 15-variable model (76% versus 83%); however, it was more successful in classifying subjects in the good outcome group (89%) than in the poor outcome group (64%).

Utilizing the seven variables shown in Table 2, we developed a prognostic scale similar to the one developed by Vaillant (1964) in his study of schizophrenics. The first four variables which had the highest correlation with outcome were given the greatest weight and scored two if present. The three others, where the strength of association was weaker, were given less weight and scored one. If a factor was absent or questionable it was scored zero. The prognostic scale score for an individual could range from zero to 11.

FIGURE 1



As shown in Figure 1, a major advantage in scaling is due to the linear rather than dichotomous nature of the relationship between prognostic scores and outcome. Subjects with scores of two or less were most likely to have good outcomes, while those with scores above four had the poorest outcomes. Subjects with scores ranging between three and four were fairly equally distributed between the two outcome groups.

Using a cutting score of two on the clinical prognostic scale we achieved a correct classification for 74% of the subjects (77% of the poor outcome group and 71% of the good outcome group). While there was little change in the overall prediction rate from the discriminant analysis (74% versus 76%), there was some loss of predictive power within the good outcome group (71% compared to 89%), and predictive ability within the poor outcome group improved slightly (77% compared to 64%).

In a series of five discriminant function analyses using our seven-variable prognostic model with a random sample of cases from the original study population, the range of correct classifications was from 72% to 78% of cases correctly classified.

DISCUSSION

The findings from this study are encouraging. The prognostic scale accurately predicted the long-term outcomes of approximately three-fourths of the alcoholic women in our sample. Considering the heterogeneity of the sample in terms of diagnostic subtypes, socioeconomic status and severity of alcoholism, as well as the relatively long (twelve year) interval between the index interview and follow-up assessment, the prediction rate is impressive.

The scale was derived using only a dichotomy (good or poor outcome), but our data (see Figure 1) indicates that our prognostic score is a linear predictor of severity of outcome; that is, the higher the score the higher the probability of poor outcome and the worse the severity of incapacitation. The lower the score the higher the probability of good outcome and the better the social and medical adjustment. These results, together with replicability of classifications in subsamples, strongly support the robustness and clincal utility of the prognostic scale.

Furthermore, in terms of the content of the scale, it is of interest to note the similarity between our scale and the one developed by Kammemeier and Conley (1979) for a mixed group of men and women. Although we were unaware of their work when our scale was developed and thus not influenced in our selection of variables, the general agreement is striking. In addition, their use of a larger sample which contained males as well as females and replication with a separate sample suggests that some of the variables have predictive power for males as well as

females and are fairly robust.

In examining the specific predictors, variables related to social stability, such as employment, marital status and socioeconomic status, are of importance in good outcome. These variables provide opportunity for intervention since they include characteristics which are amenable to change.

While further work is needed, the findings provide additional knowledge regarding prognostic factors of importance in work with alcoholic women. The prognostic scale provides an easily administered, relatively objective tool to aid clinicians in evaluating the prognosis of alcoholic women as well as suggesting targets of intervention which might increase treatment effectiveness.

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The Development of "Cross-Tolerance" Between Systemic and Spinal Morphine as a Function of the Nociceptive Assessment Test

C. Advokat and C. B. Taylor

The spinal administration of opiates has proven beneficial for the clinical management of both acute and chronic pain. One unusual aspect of this treatment is the observation that spinally injected doses which are analgesic in chronic (e.g., cancer) pain patients are comparable to doses which are analgesic in acute (e.g., postoperative) pain patients, even though chronic pain patients frequently have a history of opiate medication to which they have become tolerant. Therefore, it would be expected that they would be "cross-tolerant" to additional opiates, regardless of the route of administration. In fact, such "cross-tolerance" between systemic and intrathecal (i.th.) opiates has been demonstrated by Yaksh and his colleagues in laboratory animals, using the nociceptive hot plate test with rats. In contrast to those data we have found (Advokat and Tyler, Neurosci. Abstr. 8: 355: 1982) a lack of "cross-tolerance" between systemic and i.th. morphine using the nociceptive tail flick test. We now report that the apparent discrepancy between these previous studies is due to the assessment test. Rats that are made tolerant to systemic morphine and assessed on the hot plate (HP) are tolerant to i.th. morphine on the HP; rats that are made tolerant to systemic morphine and assessed on the tail flick (TF) are not cross-tolerant to i.th. morphine on the TF.

Male albino rats (350-400 gm) implanted with spinal catheters were assessed on the HP or TF after either morphine or placebo pellet implantation. The rats were tested daily until the latencies of the morphine-implanted rats returned to normal values, at which time they were considered tolerant. They were then examined for "cross-tolerance" by an acute injection of either subcutaneous (1-6 mg/kg) or i.th. (2.5-3.0 ug) morphine followed by a final test 40 min. later. The results showed that "cross-tolerance" between the two systemic routes of administration, subcutaneous pellets and subcutaneous injection, developed to both the HP and the TF test. In contrast, "cross-tolerance" between the systemic and the intrathecal route was only observed on the HP. Morphine-implanted animals were just as analgesic as placebo-implanted animals in their response to i.th. morphine on the TF test.

Therefore, the development of "cross-tolerance" between spinal and systemic morphine is dependent on the nociceptive test. The TF, which is a spinally mediated reflex, was not "cross-tolerant" to spinally administered morphine; whereas the HP, which is a supraspinally mediated behavior, was "cross-tolerant." This dichotomy suggests that tolerance is a function of the neural substrates that mediate both the nociceptive and pharmacological inputs. Studies are now in progress to examine the effect of chronic spinal morphine infusion on the development of tolerance to the two nociceptive tests.

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Thyroid Axis Abnormalities in Cocaine Abuse

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INTRODUCTION

Clinical manifestations of cocaine intoxication, such as increased energy, psychomotor activation, diaphoresis, hyperthermia, and cardiovascular arousal are remarkably similar to hyperthyroid states. Conversely, the abrupt cessation of cocaine abuse often results in symptoms resembling hypothyroidism, such as anergia, depression, psychomotor retardation, hypersomnia, and weight gain. Morley et al. (1980) found that monkeys acutely and chronically exposed to dextroamphetamine had elevated thyroid hormone (T_4) and thyroid stimulating hormone (TSH), further linking stimulant intoxication with thyroid axis activation. Also reported (Morley et al. 1980) were four cases of amphetamine-abusing patients with elevated T_4 levels. Mantegazza et al. (1968) found reduced toxicity of amphetamines in hypothyroid compared with euthyroid rats, again suggesting a potentiation of the thyroid axis by central stimulants. This present study is the first report of cocaine-induced thyroid axis alterations in man.

Cocaine has well established potentiating effects on central norepinephrine (NE) and dopamine (DA) systems in the brain (Langer and Enero 1974; Ross and Renyi 1966). Besses et al. (1975) suggested that DA neurons are involved in the regulation of TSH secretion because they found that DA infusions in normal men inhibited the TSH response to thyrotropin-releasing hormone (TRH). Reichlin (1975) reported release of TRH after hypothalamic infusion of DA and NE, but attributed the DA effect to its conversion to NE. Serotonin was found to inhibit TRH release, leading to the conclusion that TRH secretion is stimulated by NE neurons and inhibited by serotonin neurons (Reichlin 1975). Since cocaine produces numerous disruptions in serotonin, NE and DA neuronal function (Dackis and Gold 1984), thyroid axis disruptions secondary to chronic cocaine abuse are plausible.

In order to assess the effects of chronic cocaine abuse on the thyroid axis, we studied hospitalized cocaine patients with the TRH test. This test is the most sensitive measure of thyroid axis function (Saberi and Utiger 1975; Jackson 1982). This test was also selected because of its wide use as a diagnostic test for depression (Extein et al. 1982). Specific TRH testing for depression of cocaine-abusing patients would depend upon normal TRH test results in non-depressed cocaine abusers. Therefore we designed this study to assess both the diagnostic reliability of the TRH test for depression in cocaine patients, and the effect of chronic cocaine abuse on the thyroid axis.

METHODS

We studied 17 consecutive patients admitted with cocaine abuse by DSM III criteria, and with confirmatory plasma or urinary cocaine titers (Kim and Cereo, 1976) demonstrated at the time of admission to a locked hospital ward. Patients were excluded if they met DSM III criteria for other substance abuse, dependence, or for major affective disorders. Twenty normal controls, similar in age and sex, and without substance abuse or major affective illness, were also studied. Each subject received a TRH test as previously described (Extein et al. 1982), with baseline T_3 and T_4 levels by radioimmunoassay. Cocaine patients received TRH testing during their first week of hospitalization. The TSH response to TRH (500 ug IV) was calculated as peak minus baseline TSH (Δ TSH).

RESULTS

There were no significant differences in baseline T_3, T_4 and TSH between the two groups. However, the TSH scores of cocaine patients (7.4 $\pm$ 3.3 uIU/ml) were significantly lower ($p < 0.001$, df=35, $t=4.59$) when compared to the controls (13.4 $\pm$ 4.2 uIU/ml). In addition, 8 of 17 cocaine patients (47%) had a blunted Δ TSH (<7 uIU/ml) (Extein et al. 1982), compared to none of the controls (Chi Square (1) = 9.27, $p < 0.01$).

DISCUSSION

Our data demonstrate inadequate TSH responses to TRH in patients with cocaine abuse. This finding is consistent with our present knowledge regarding TRH regulation by biogenic amines. Direct hypothalamic administration of NE and DA result in TRH release. Chronic cocaine abuse could lead to chronically elevated TRH, down regulation of the receptors for TRH in the anterior pituitary, and subsequent blunting of the TSH response to TRH. This response is exquisitely sensitive to thyroid axis changes and involved in the maintenance of homeostasis (Saberi and Utiger 1975). Cocaine intoxication could produce a state of compensated hyperthyroidism which is only evident on TRH testing. (See Figure 1).

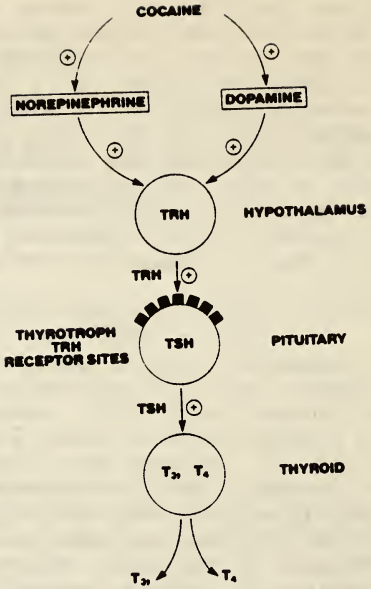

Fig 1. Chronic cocaine abuse is hypothesized to produce chronically elevated TRH levels through DA and NE stimulation, with compensatory down-regulation of TRH receptor sites. Abrupt discontinuation of cocaine would produce a relatively hypothyroid state due to TRH receptor subsensitivity and the lack of TRH stimulation.

While cocaine intoxication could produce thyroid axis activation by releasing TRH, the sudden cessation of cocaine use might result in thyroid axis inhibition due to the presence of desensitized thyrotroph TRH receptors. Thyroid axis inhibition at the level of the pituitary thyrotroph was found in our cocaine patients, and could make a major contribution to the neurovegetative symptoms associated with the cessation of cocaine abuse. Reversal of cocaine abstinence symptoms may depend upon the normalization of the thyroid axis and neuronal regulatory systems.

Due to the profound blunting of the TRH test in non-depressed cocaine abusers, this test is not suitable as a diagnostic test for depression in these patients. In fact, subtle mood disturbances seen after the cessation of cocaine use may result from thyroid axis alterations. Neuroendocrine disruptions apparently result from neurotransmitter effects of cocaine, and represent homeostatic imbalance. Disruptions in brain homeostasis by cocaine can be conceptualized as evidence of "physical addiction" and may explain the profound difficulty experienced by these patients as they attempt to remain free of cocaine.

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Non-Dividing Human Lymphocytes Have Specific Binding Sites for Naloxone

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Human lymphocytes were obtained (courtesy of the Atlanta Chapter of the American Red Cross) from the leukocyte-platelet fraction of a blood plateletpheresis procedure. After centrifugation on Ficol-Paque the monocytes were removed from the mononuclear leukocytes by absorption on plastic and glass wool, leaving a lymphocyte fraction that was greater than 90% T lymphocytes and less than 10% B and NK cells. Binding of ^{3}H-naloxone to these cells was measured by an equilibrium, glass filter assay with non-radioactive naloxone as the competing ligand. After removal of the monocytes, non-specific binding was markedly reduced and a reproducible, saturable, competitive binding of ^{3}H-naloxone was found. Purified lymphocytes from two subjects yielded K_D's of 10.0 and 9.3 nM with a mean of 9.7 nM. There was a high degree of cooperativity of binding. A Hill plot of the data for each individual produced n's of 2.43 and 1.99 respectively for a mean value of 2.21. While K_D and n did not vary significantly between samples, the apparent number of binding sites per cell varied considerably, with the two cell preparations yielding values of 6620 and 3750 sites per leukocyte respectively ($u = 5185$). Whether this variance is a product of genetic and/or environmental factors controlling binding site expression, or whether variation in binding site density on specific lymphocyte subpopulations is responsible has not yet been ascertained. If the former explanation is relevent, then individual subject variation in binding site number may be important in defining the differential responses of individuals to opiates. On the other hand, if binding site density varies between different T lymphocyte populations, then differences in cell populations between individuals could explain the variation in binding sites/cell found. A difference in

binding site density between suppressor and helper T cells might explain the selective loss of helper T cells found in opiate addicts. Regardless of the reason for the binding site density variation, measurement of opiate binding to purified leukocyte population is critical to understanding the mechanisms by which opiates alter the biological properties and activity of the human immune system.

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Effects of Diazepam on Affective Properties of Memories

R. E. Mann; B. A. Nicholls; C. A. Naranjo; C. W. Mueller; and H. D. Cappell

Benzodiazepines have been shown to have reinforcing effects for both humans and animals (Bigelow et al. 1976; Yanagita 1976). One possible approach to understanding their reinforcing effects is based on the drugs' therapeutically useful property of mood modification, which may serve as a functional basis for reinforcement (e.g., Johanson and Uhlenhuth 1980). A better comprehension of the nature of these mood-modifying effects may have important implications for our understanding of the mechanisms by which these drugs produce abuse.

Recently, it has been shown that memories which are affectively congruent with a naturally occurring or behaviourally induced mood state are recalled faster and more often than affectively incongruent memories. Teasdale and colleagues (Teasdale and Fogarty 1979; Clark and Teasdale 1982) have developed a procedure to demonstrate this effect. Subjects are shown a series of common words and are asked to think of a memory (some event which they have experienced) for each word. Subsequently, the subjects are asked to rate the memory on affective dimensions (e.g., how happy/unhappy the event made them feel). Memories elicited during periods when subjects are depressed (either naturally occurring or induced) are rated as more unpleasant or unhappy than are memories elicited when subjects are not depressed. The present study examined the usefulness of such a procedure for assessing the mood-modifying effects of diazepam.

METHOD

The subjects were sixteen male and sixteen female university students between 19 and 32 years of age. A history was taken to exclude heavy users of alcohol or drugs. All subjects received 10 mg. oral diazepam and a placebo on separate days, in a double-blind, counterbalanced design. The task adapted from Teasdale's work was called the cue-word task. Each time this task was performed, subjects were presented with a series of twenty common words (e.g., village, cloud). For each word, they were required to think of a specific memory (i.e., an event which occurred to

them in the past) which was evoked by the word. They then wrote down a short description of the memory, which would allow them to recall it later, before viewing the next word in the series.

At the beginning of each session, prior to receiving drug or placebo, subjects provided measures of anxiety and verbal free recall, in addition to performing the cue-word task. Verbal free recall measures were also obtained 30, 60, and 120 min. after administration of drug or placebo. The cue-word task was re-administered (with different words) at the 60 min. test, when peak drug effects were expected to occur (Sellers and Busto 1980). At the end of each session (180 min. after receiving drug or placebo) subjects rated the memories evoked by the two administrations of the cue-word task on that day. Each memory was scored on each of six dimensions: 1) how unhappy-happy the event made them feel when it occurred (Happy-Then); 2) how unhappy-happy the memory makes them feel when they think about it now (Happy-Now); 3) how unpleasant-pleasant the event made them feel when it occurred (Pleasant-Then); 4) how unpleasant-pleasant the memory makes them feel when they think about it now (Pleasant-Now); 5) how anxious-relaxed the event made them feel when it occurred (Anxious-Then); and 6) how anxious-relaxed the memory makes them feel when they think about it now (Anxious-Now). At the end of the second day of testing, subjects were also asked to guess on which day they had received the active drug and to fill out a brief drug-liking scale.

RESULTS AND DISCUSSION

Variance analysis of the free recall data demonstrated that subjects recalled significantly fewer words after administration of diazepam than after administration of placebo. This result replicates previous observations, and confirms that the dose of diazepam used in the present study influenced the memory processes of the subjects. Variance analyses of the cue-word data revealed several drug effects on that task. Significant ($p < .05$) or marginally significant ($.05 < p < .10$) main effects of drug were found on all of the six rating scales. In every case, memories on the drug day were rated as more positive (i.e., happier, more pleasant, more relaxed both then and now) than memories on the placebo day. As well, significant or marginally significant Drug X Sex X Trial interactions were observed for the Happy-Then, Happy-Now, Pleasant-Then, and Pleasant-Now scales. Further analyses of these interactions suggested that females were more influenced by diazepam than males. The reasons for these sex differences are not yet known. Analyses of the drug-liking data revealed no sex differences. Interestingly, subjects of both sexes tended to dislike the effects of the drug, suggesting that the positive effects of diazepam on affective qualities of memories are independent of subjective enjoyment of the drug experience.

In summary, memories generated on days when diazepam was administered were given significantly more positive ratings than those generated on placebo days. As well, these effects were more

pronounced for females than males. For both sexes, the positive effects of diazepam on the affective qualities of memories were independent of self-reported liking of the drugged state. The results are consistent with the known anxiolytic properties of diazepam, and demonstrate that such effects occur in subjects not selected for high anxiety levels. The present research demonstrates the sensitivity of these measures to drug-induced manipulations of mood; the data also suggest that the cognitive and affective changes induced by diazepam are interdependent.

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In the interests of space limitations all references can be obtained from the senior author.

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Alcoholics' Responses to Drinking Cues

R. E. Mann; C. X. Poulos; H. L. Kaplan; R. E. Hinson; M. Paunil; P. J. Iversen; and H. D. Cappell

Many have suggested that conditioning processes may play a role in tolerance to, and dependence on, alcohol and other drugs (e.g., Grabowski and O'Brien 1981; Wikler 1980). One model for the role of conditioning processes in alcohol and drug influenced behavior has been described by Siegel (1975; 1977) and others. According to the model, drug administration elicits an unconditioned compensatory response which is opposite in direction to the drug effect. Over training, the compensatory response becomes conditioned to environmental stimuli which reliably precede drug administration. After repeated pairing of drug administration with environmental cues, administration of the drug evokes the conditional compensatory response, which counteracts some or all of the drug's effects, resulting in tolerance. When cues associated with drug administration are presented without drug administration, the conditional compensatory response alone is elicited. It has been suggested that the elicitation of compensatory responses in the absence of the drug may contribute to the craving experienced by alcoholics and other drug abusers. Thus, extinction of this response may assist the alcoholic in overcoming urges to drink.

The conditional compensatory response model has received substantial support from animal research. The two experiments reported here were designed to test predictions of the model in human subjects. In both experiments, alcoholics were exposed to stimuli associated with alcohol consumption (i.e., they were exposed to, and consumed, a nonalcoholic malt beverage which looked, smelled and tasted like beer) and responses on several psychophysiological and behavioral indices were measured.

EXPERIMENT 1

Twenty-four male alcoholic volunteers from a detoxification center served as subjects. Participants were between 20 and 50 years of age; all reported experiencing withdrawal symptoms after cessation of drinking. Subjects were led to believe that they might be asked to consume an alcoholic beverage; otherwise they were given a complete description of the study. After equipment

set-up and adjustment in a psychophysiological laboratory, each subject was seated in a comfortable chair and the experimental procedures began. These procedures consisted of exposing the subject sequentially to alcohol consumption cues and water consumption cues (order of presentation was counterbalanced across subjects).

Each condition began with a 10-min. Baseline period. This was followed by a 10-min. Cues period. For the alcohol cues condition, a tray containing liquor and beer bottles was brought into the room; for the water cues condition, the tray contained a pitcher of water. The 10-min. Drinking period followed. Subjects were asked to drink a glass containing either 5 oz. of the beer-like malt beverage or water, respectively. At the end of this period, the tray was removed from the room. Two 10-min. periods (Post-Drink 1 and Post-Drink 2) followed next to allow measurement of any responses elicited by the beverage. The Baseline period for the second beverage began immediately after the Post-Drink 2 period for the first beverage. Several psychophysiological measures, as well as measures of craving, anxiety, verbal memory, and coding performance, were collected throughout the study.

Variance analyses of the data revealed several significant ($p < .05$) or marginally significant ($.05 < p < .10$) changes associated with presentation of the alcohol cues (only some of which will be presented here). Craving scores did not differ between the water and alcohol cues conditions in the Baseline period, but significant elevations in craving were observed after exposure to the alcohol cues. The mean heart rate decreased over time periods; however, this trend was interrupted by a temporary increase after exposure to the alcohol cues. Skin temperature also decreased over time periods, interrupted by a temporary increase after exposure to the alcohol cues. The amplitude of the T-wave increased over the first three time periods; in the Post-Drink periods this increase continued in the water cues condition, while in the alcohol cues condition the T-wave amplitude began to decrease.

EXPERIMENT 2

Twenty (out of a planned twenty-four) male alcoholic volunteers have completed the second experiment. Subject population, general design, procedures, and dependent measures were the same as those described for Experiment 1. To examine extinction, on each of four consecutive days subjects were exposed to 10 min. Baseline, Cues and Drinking conditions exactly like those in the alcohol cues condition in Experiment 1. A single 10-min. Post-Drink period was also included on each day. Additionally, half of the subjects were exposed to three additional presentations of the alcohol consumption cues on each day; these data will not be described here.

Significant or marginally significant changes in response patterns

over days for the heart rate, skin temperature, and T-wave amplitude measures have been observed. On the first day the patterns of responding were very similar to those seen in the alcohol cues condition of Experiment 1. However, by the fourth day, the patterns of responding resemble those observed in the water cues condition of Experiment 1.

DISCUSSION

The results of the first study revealed changes in several of the indices after a single exposure to alcohol consumption cues, but not after water consumption cues. These changes are consistent with elicitation of a conditional compensatory response by the alcohol consumption cues. The second study tested the hypothesis that these responses will extinguish with repeated exposures to the alcohol consumption cues. Preliminary analyses indicate that initial exposures to the alcohol consumption cues result in changes similar to those observed in the first experiment. However, these changes do not persist after repeated exposures to the cues. These data, then, support the conditioning interpretation by indicating that extinction of the response to the alcohol cues may have occurred over the four days of the experiment.

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Characteristics of Drug-Dependent Mothers Who Participate in Developmental Outcome Studies of Their Infants

Dianne O'Malley Regan; Theresa Matteucci; Joyce Diodati; Karol Kaltenbach; and Loretta P. Finnegan

Family Center is a comprehensive program which provides obstetrical, psychosocial, and methadone maintenance for pregnant drug-dependent women. In conjunction with this program, there is a 5-year longitudinal research project investigating the developmental and neurological outcome of infants at periodic intervals throughout the first five years of life. From 1980 to 1982, 67 methadone-maintained mothers enrolled in this program agreed to have their infants evaluated at 6, 12, 18, 24, 36, and 48 months of age. Twenty-three of these mothers did not return with their infants to be tested at 6 months of age and thus had to be dropped from the study. To determine if there were any salient characteristics between participants (Group I) and non-participants (Group II), the following maternal variables were examined: 1) number of prenatal visits, 2) continued enrollment in the program, 3) race, 4) age at delivery, and 5) percentage of urines containing illicit drugs. Severity of neonatal abstinence was also examined.

Mothers who participated in the follow-up study did not differ from non-participating mothers in age at delivery, race, or incidence of illicit drug use. There were no significant differences found between the two groups of mothers in severity of neonatal abstinence, both in terms of whether the infant required pharmacotherapy or duration of infant hospitalization. However, participating mothers were found to have more prenatal visits ($t=2.11$, $p < .05$), and were more likely to be currently enrolled in the program ($x^2=9.4$, $p < .01$) than non-participating mothers.

One of the major problems confronting research designed to investigate the developmental outcome of children born to drug dependent mothers is subject participation. These data indicate the importance and value of integrating research within the framework of clinical services for this population.

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Hypothalamic-Pituitary-Adrenal Axis Function and Behavioral Reactivity to Stress in Adult Rats Administered THC in Early Life

J. A. Rosecrans; S. E. Robinson; M. K. Etkin; D. J. Mokler; J. H. Johnson; and J. -S. Hong

The major objective of this research was to determine the long-term effects of Δ^9-tetrahydrocannabinol (THC) on the hypothalamic-pituitary-adrenal-axis (HPAA) function. To accomplish this objective, rats were administered 3 dosage regimens of THC (10 mg/kg, sc) between 30 and 50 days of age: 20, 10, and 5 doses dissolved in emulfor vehicle were administered. Dosages were interspaced equally over a 20-day period and all rats received 20 daily doses of either THC or vehicle. Dosage regimens were chosen to simulate human dosage patterns of chronic, heavy, and occasional use. Two strains of rats were used in this study: Sprague-Dawley (CD) and Fischer-344 (CDF).

Adult (135 days of age) CD and CDF rats were exposed to a stress-induced analgesia paradigm (FSIA), consisting of 15 sec of 1.5 mA foot shock. Half of the rats of each treatment (TRT) group served as controls. Tail-flick latencies (tail-withdrawal from warm water, 55°C) were measured before and after foot-shock on day 1 in order to evaluate the effects of acute FSIA in each TRT group. Foot shock exposure was continued for an additional 3 daily sessions in which latencies were measured only prior to foot-shock as a means of evaluating the development of conditioning to the shock (autoanalgesia). Extinction of the conditioned response to shock was evaluated 2, 7, 14, 21, and 28 days after the last shock exposure. Tail-flick latencies were measured with rats on the shock grid previously associated with shock. CDF rats were sacrificed 15 min after exposure on day 28 and plasma collected for the evaluation of HPAA function; corticosterone (CS) and prolactin (PRL) were evaluated using RIA. CD rats and sham controls were evaluated for an additional two weeks using classical operant behavioral techniques.

All rats exposed to acute foot shock exhibited an analgesic response; CDF rats were significantly more responsive to this stress. The acute response to foot shock was also significantly facilitated by THC (10 X THC) when administered postweaning ($P = 0.033$; Fisher's Exact Probability Test). In addition, all rats developed conditioned analgesia to foot-shock; there were few differences between TRT groups. The most significant findings in this research were in relation to plasma PRL levels (Table 1). ANOVA evaluations indicated

a significant relationship between stress vs. nonstressed rats ($P < 0.0052$, $F=8.75$) in relation to plasma CS levels, but there were no significant treatment interactions. An evaluation of plasma PRL levels indicated both a group ($P < 0.0008$; $F=13.30$) and a TRT X Group interaction ($P < 0.0433$; $F=3.00$). An interpretation of these data is difficult at this time but it seems that the significant interaction occurred as a result of a combination of effects of the 10 X THC and 5 X THC. Both postweaning treatments appeared to have the effect of increasing the sensitivity of the conditioning effects of foot shock while lowering ambient PRL levels of control rats receiving THC in early life. Interestingly, the 20 X THC had little effects on any of the parameters measured. These studies provide evidence that THC, when administered postweaning, had potential long-term effects when such rats are exposed to stress as adults. Rats receiving 10 X or 5 X THC over a 20-day period seemed to be more affected in adulthood.

TABLE I: EFFECT OF VARIOUS POSTWEANING THC DOSAGE REGIMENS ON HPAA FUNCTION.

Parameters	Vehicle	5 X THC	10 X THC	20 X THC
Plasma CS				
Control:	83 ± 17[1]	134 ± 21	99 ± 52	112 ± 22
Stress:	142 ± 34	179 ± 30	215 ± 42	143 ± 41
Plasma PRL				
Control:	127 ± 50	34 ± 5	33 ± 2	99± 54
Stress:	171 ± 44	287 ± 92	314 ± 94	118 ± 35

[1]Values are mean ± S.E.M. (n=6) in ng/ml plasma.

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Equi-Analgesic Dose Models for Quantitative Physical Dependence Assessment in the Mouse: Single Dose Suppression, Precipitated Abstinence, and Primary Dependence Induction Tests

William K. Schmidt

ABSTRACT

Quantitative methods have been developed to measure the physical dependence-producing properties of narcotic-related analgesics in the mouse. Included are a Single Dose Suppression (SDS) test and a Precipitated Abstinence (PA) test in morphine-dependent mice and a Primary Dependence Induction (PDI) test in naive mice wherein equieffective dose levels of selected analgesics are maintained by continuous minipump infusion. Major advantages include: 1) the ability to assess dependence potential at analgetic ED50 doses, 2) using the same species for both analgesia and dependence assessment, and 3) the development of a highly reliable computer-based method for quantitating withdrawal jumping activity in up to 64 animals simultaneously for periods from 5 min to 8 hr, then rapidly analyzing the data and producing detailed reports of withdrawal activity.

Results indicate that mu-agonist analgesics produce high levels of dependence in all tests. Kappa-agonist analgesics produce minimal or no dependence. Agonist/antagonist analgesics are heterogeneous, producing effects that are either mu-or kappa-like depending on the drug used. Of all agonist/antagonist and kappa-agonist analgesics, only nalbuphine, nalorphine, tifluadom, and U-50,488H produced no abrupt abstinence withdrawal after 72 hr continuous infusion (PDI test). Similarly, these drugs produce minimal or no suppression of withdrawal in partly-withdrawn morphine-dependent mice (SDS test). Analgesic-range doses of nalbuphine and nalorphine precipitate intense abstinence responses in non-withdrawn morphine-dependent mice (PA test). Drugs with weaker antagonist activity (pentazocine, butorphanol, buprenorphine) require much larger doses to precipitate withdrawal.

These procedures offer a highly quantitative and comparatively rapid (<1 week, all tests) assessment of the physical dependence liability of narcotic-related analgesics with a high predictability to man.

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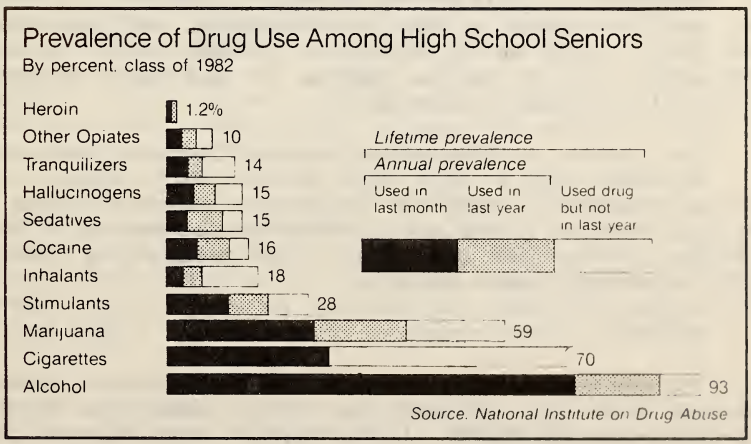
Adolescent Cocaine Abuse

Linda Semlitz and Mark S. Gold

INTRODUCTION

The incidence of adolescent cocaine abuse is increasing faster than any other drug (Kandel 1982). Surveys report that a total of 22 million Americans (NIDA 1982) have tried cocaine and the numbers continue to rise. According to the 1983 National Institute of Drug Abuse (NIDA) sponsored survey of 17,000 high school seniors, the use of marijuana and other drugs has decreased since 1978 (American Medical News 1984). PCP rose slightly from 2% to 3%. Daily use of marijuana has declined from 10.7% in 1978 to 5.5% in 1983. The annual prevalence of marijuana use decreased from 51% in 1979 to 42% in 1983. Nearly 63% of the seniors admitted trying an illicit drug other than marijuana at some time, down from 66% in 1982. Although 86% of the seniors said they could procure marijuana, 61% said that they disapproved of occasional marijuana use while nearly 83% said they disapproved of regular marijuana use. In marked contradistinction, the number of people who tried cocaine nearly doubled, from 9% in 1975 to 17% in 1983. Figure 1 reviews drug-taking behavior of the high school class of 1982. (Figure 1) 3% of 1981 high school seniors used cocaine daily in the month prior to being surveyed. (Figure 2).



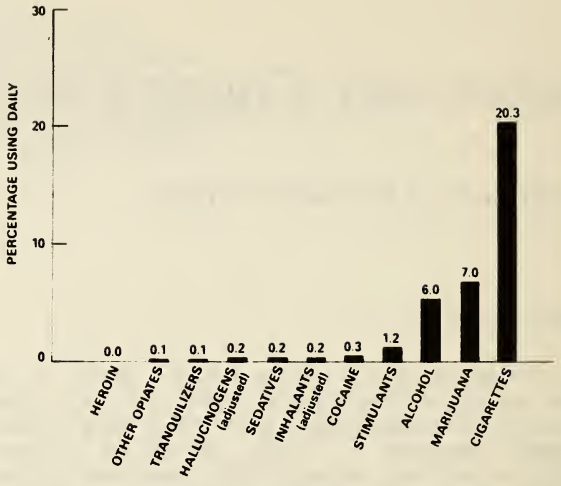


FIG. 2. Thirty-day prevalence of daily use of 11 types of drugs, class of 1981. (Source: Johnston et. al. (1981).)

Drug-using youth demonstrate a variety of problem behaviors including low self-esteem, impulsiveness, negative attitudes toward school, and low academic aspirations. Childhood aggression and rebelliousness predict later dysfunction. Behavioral correlates most frequently associated with other problem behaviors are school discipline problems, delinquent behavior, all types of antisocial behavior and frequent use of cigarettes, alcohol and other drugs (Narem-Heisen and Hedin, 1983). More importantly, drug use is an important cause of mortality via motor vehicle accidents and death by suicide. Tragically the drug-abusing group is less likely to seek help. The belief that adolescents do not abuse cocaine because of age, lack of access to hard drugs, or of financial inaccessibility is not supported by objective data. Clinicians need to be able to identify the symptoms resulting from cocaine abuse early on in order to prevent future morbidity and mortality. It is the purpose of this paper to profile the typical regular cocaine user.

In response to the recent national increase in cocaine abuse problems, Mark S. Gold, M.D., and Fair Oaks Hospital established a national telephone helpline, 800-COCAINE, to provide information, advice, and referral to treatment on a 24-hour per day, 7-day per week basis. We conducted a survey of 60 adolescent cocaine abusers.

METHODS

Our subjects were 60 cocaine abusers randomly selected from calls in June 1983 and from 30,000 callers in February 1984. Subjects had learned of the helpline from radio and television broadcasts stating that 800-COCAINE could be called anonymously

from anywhere in the United States to obtain information or referral to treatment for a cocaine problem. Each subject voluntarily consented to a 20-30 minute confidential telephone interview conducted by an experienced drug abuse counselor. Questionnaires were completed that included demographic data drug use patterns, and negative medical and psychosocial effect. While we have received calls from every state, the callers in this sample were primarily from NY/NJ (25%), California (20%), Illinois (12%), and Pennsylvania (8%). The sample consisted of 28 females and 32 males with a mean age of 17 years. Fifty-four (90%) were white and 10 were black or Hispanic.

RESULTS

The natural history of progressive cocaine abuse is rapid. The time course between snorting their "1st line" and deterioration in functioning leading to a call to the helpline is only 15 months, compared to 4-1/2 years in adults (Washton et al. 1984). Despite it's cost, adolescents have access to cocaine typically by either dealing drugs or by becoming sexually involved with a more financially secure user. Of the 60 callers, 85% were intranasal (IN) users, 8% were freebase smokers (FB), and 7% used cocaine intravenously (IV). While all were self-proclaimed problem users only 48% used cocaine on a daily basis. Among the FB and IV users, All had started using cocaine by the intranasal route. The average caller was a 17-year-old with 11 years of education who uses cocaine by nasal inhalation and who views himself or herself as addicted.

At a street cost of $75-125 dollars per gram, callers reported spending from 0-$5000, with an average of $440/month. The average caller cited 12 of 22 negative psychiatric effects. The adolescents were typically jittery (70%), chronically anxious (78%), and depressed (68%), with acute psychiatric symptoms secondary to heavy cocaine use characterized by delusions (35%), suspiciousness (70%), paranoia (72%), and compulsive behavior (73%). Cognitive impairment included poor concentration (65%), and memory defects (63%). 48% lost interest in their friends and 62% lost interest in non-drug related activity. Twenty-eight percent had active thoughts of suicide, and 12% reported a suicide attempt.

The typical caller reported 11 of 22 possible questionnaire items for adverse physical effects. The most commonly cited physical symptoms included sleep difficulty (78%), chronic fatigue (68%), runny nose (72%), and sinus problems (63%). Intranasal users reported palpitations (65%) and nausea and vomiting (50%). Twenty percent reported seizures.

Adolescent cocaine abusers suffered alarming social and financial consequences. 42% deal drugs, and 35% resort to other illicit activity to obtain cocaine. 20% have been arrested,

33% suffer school problems, and 18% have either been suspended, expelled, or fired from part-time employment, 52% report a loss of friends and 75% report fighting or violent arguments, 43% are in debt, and 38% have stolen as a direct result of their cocaine use. 12% of 18- and 19-year-olds suffered traffic accidents. In spite of these consequences, 82% state that they continue to use cocaine in order to recreate the original high.

There has been a debate for some time whether cocaine is addicting with an assumption that non-addiction means absence of danger. A more useful definition of addiction is compulsive continued use in the face of obvious negative consequences. In addition adolescents do not have the experience or judgement to compensate for their behavior while intoxicated. Although (67%) feel the medical consequences of cocaine use are moderate to severe, only 10% stopped use because of such effects. Chronic use typically leads to chronic depression, fatigue, and irritability. Peak use of cocaine occurs at a time when youth must make commitments to family and work roles and negotiate a firm self-image. Drug use is an identity, life style and 24 hour/day job. Delays in psychosocial and interpersonal development are common. Consistent with other studies (Single et al. 1974), this study suggests that users of cocaine and other illicit drugs are less conforming than non-users, with resulting school problems, absenteeism, increased frequency of delinquent acts involving interpersonal aggression, theft, traffic violations, and other vehicle accidents and accidental death by suicide. Unfortunately, the family is typically late in correlating social and moral decay to drug use.

DISCUSSION

In summary, we have profiled the typical regular cocaine user as a 17-year-old 11th grader who is chronically irritable, depressed, estranged from family and friends, doing poorly academically, and suffering from sleeplessness, weight loss, rhinitis and of more concern occasionally seizures. The time between first use and marked deterioration is 15 months. Freebase and intravenous use was also preceded by intranasal use. There is no specific treatment for cocaine abuse with demonstrated long-term efficacy. The first task of treatment is to get the patient and family to think that treatment is necessary. Frequently adolescents are pressured into treatment with clinicians who do not know about drug use (they neglect to tell them) and/or do not have drug abuse experience. Using psychotherapy while the individual continues to abuse prolongs the addictive process and provides the user with a rationalization that he is seeking help. Psychotherapy should occur only after substance abuse has totally stopped. Supportive counseling, peer support groups, family education and urine monitoring seem to be essential for treatment.

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Comparison of Physical Dependence-Producing Mechanism Between Barbiturates and Benzodiazepines

Yoshio Wakasa; Shin Kato; and Tomoji Yanagita

It is well known that benzodiazepines produce physical dependence of the barbiturate type and that the withdrawal signs of the drugs are similar to those of barbiturates in human (Hollister 1961; Essig 1964) and in animals (Yanagita and Takahashi 1973). Further, benzodiazepines are known to suppress barbital withdrawal signs, indicating that they possess cross-physical dependence property to barbiturates (Deneau 1977; Yanagita and Takahashi 1973). Thus, benzodiazepines and barbiturates appear to share, at least partially, some common mechanism to produce physical dependence.

Since it is known that while benzodiazepines act through the benzodiazepine receptors, barbiturates do not, and that specific benzodiazepine antagonists such as Ro15-1788 antagonize to the central nervous system effects of benzodiazepines at the receptor site (Darragh et al. 1981; Hunkeler et al. 1981) and precipitate withdrawal signs in benzodiazepine-dependent animals (McNicholas and Martin 1982; Lukas and Griffith 1982; Rosenberg and Chiu 1982), involvement of the benzodiazepine receptors in the physical dependence-producing mechanisms of benzodiazepines and barbiturates were studied in the rhesus monkeys physically dependent on diazepam or barbital.

METHODS

Route of Administration of Drugs and Dose of Ro15-1788

All drugs were administered intragastrically by gavage with exception of pentobarbital which was administered intramuscularly. The dose of Ro15-1788 was always 10 mg/kg.

Severity Scores of Withdrawal Signs

The severity of withdrawal signs in the monkeys physically dependent on barbital or diazepam was scored according to the criteria shown in Table 1.

TABLE 1 SCORING SYSTEM FOR WITHDRAWAL SIGNS

Withdrawal Signs	Points	Criteria
Apprehension Hyperirritability, and Restlessness	Mild : 1	Elicited when man touches
	Intermediate : 2	Elicited when man approaches
	Severe : 3	Elicited even when man stands outside the cage
Salivation	Mild : 1	Observed around the mouth
	Intermediate : 2	Dropping sometimes from the mouth
	Severe : 3	Dropping frequently from the mouth
Piloerection	Mild : 1	Observed in the shoulder
	Intermediate : 2	Observed in the shoulder and the back
	Severe : 3	Observed in the whole body
Tremor	Mild : 2	Observed in fingers when moving
	Intermediate : 4	Observed in fingers and limbs when moving
	Severe : 6	Observed even when sitting
Muscle rigidity (abdomen)	Mild : 2	Periodic rigidity by palpitation
	Intermediate : 4	Continuous rigidity
	Severe : 6	Agonizing response elicited by palpitation
Motor impairment	Mild : 2	Slow motion
	Intermediate : 4	Falls from the perch occasionally
	Severe : 6	Cannot jump
Retching or Vomiting	Mild : 2	Observed once for 30 min
	Intermediate : 4	Observed 2 to 4 timmes for 30 min
	Severe : 6	Observed more than 5 times for 30 min
Lying down	Mild : 2	Observed sometimes
	Intermediate : 4	Interrupted when man approaches
	Severe : 6	Interrpted when man touches
Quarreling	Mild : 2	Threatening observers or fellow monkeys sometimes
	Intermediate : 4	Threatening observers or fellow monkeys
	Severe : 6	Attacking observers or fellow monkeys
Defecation	Mild : 2	Observed sometimes
	Intermediate : 4	Soft feces observed
	Severe : 6	Diarrhea observed
Convulsion	6	

Experiment 1. The Effect of Ro15-1788 in Barbital-Dependent Monkeys

Seven female rhesus monkeys were treated with repeated dose of barbital 75 mg/kg once daily for first week then twice daily for other 7 weeks. Two and a half hours after the last dose of barbital, Ro15-1788 to 4 monkeys and carboxymethylcellulose-Na vehicle 2 ml/kg to 3 monkeys were administered by gavage and withdrawal manifestation was observed for 3 hours.

Experiment 2. The Effect of Ro15-1788 in Barbital-Dependent and Diazepam-Substituted Monkeys

Six female monkeys treated with barbital for total 8 weeks, 2 of which were those used in Experiment 1, were withdrawan for about 50 hours, then received single dose of diazepam 4 mg/kg. Two and a half hours later Ro15-1788 and the vehicle were administered to 3 monkeys each and the changes in severity of withdrawal signs were observed for 3 hours.

Experiment 3. The Effect of Ro15-1788 in Diazepam-Dependent Monkeys

Six female monkeys were treated with diazepam twice daily at doses of 8 mg/kg in the first 2 weeks then at 12 mg/kg in the second 2 weeks. Two and a half hours later after the last dose of diazepam single doses of Ro15-1788 and the vehicle were administered to 4 and 2 monkeys respectively and withdrawal manifestation was observed for 0.5 to 2 hours in the former and for 1 week in the latter.

Experiment 4. Influence of Pentobarbital-Na Pretreatment on the Effects of Ro15-1788 in Diazepam-Dependent Monkeys

Four monkeys used in Experiment 3 were treated further with diazepam 12 mg/kg twice daily for 6 weeks. Two and a half hours later after the last dose of diazepam, pentobarbital-Na 15 mg/kg or saline were administered to 2 monkeys each, then 5 minutes later all monkeys received Ro15-1788 and withdrawal manifestation was observed for 3 hours. The experiment was repeated with further 4-week administration of diazepam and by crossing over the animals for pentobarbital-Na and the vehicle.

RESULTS

Experiment 1. The Effect of Ro15-1788 in Barbital-Dependent Monkeys

One monkey showed vomitings within a few minutes after administration of Ro15-1788. No other meaningful sign was observable by administration of Ro15-1788 or the CMC vehicle.

Experiment 2. The Effect of Ro15-1788 in Barbital-Dependent and Diazepam-Substituted Monkeys

Upon withdrawal of barbital for about 50 hours the monkeys manifested such signs as apprehension, hyperirritability, tremor, muscle rigidity, and impaired motor activity. By administration of diazepam 4 mg/kg these withdrawal signs attenuated or disappeared within an hour; however, the signs exaggerated or reappeared when Ro15-1788 was administered to them. No exaggeration or reappearance of the signs was observed with the vehicle at least for 1 hour after administration (Fig.1).

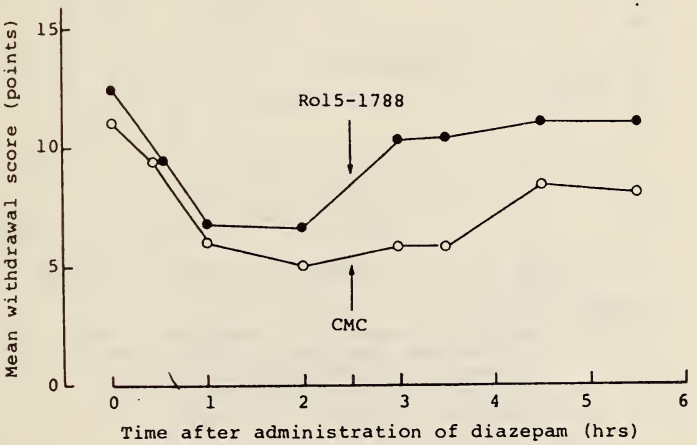

FIGURE 1 Diazepam 4 mg/kg was administered about 50 hours after the last dose of barbital and 2.5 hr later, Ro15-1788 (●) and control (CMC) (○) were administered to 3 monkeys each. The barbital withdrawal signs suppressed by diazepam were precipitated by the benzodiazepine antagonist.

Experiment 3. The Effect of Ro15-1788 in Diazepam-Dependent Monkeys

Within a few minutes after administration of Ro15-1788, the monkeys began to manifest such withdrawal signs as restlessness, lying on perch, salivation, retching, and vomiting, and thereafter, defecation, diarrhea, muscle rigidity, tremor, impaired motor activity, and threatening or attacking of other monkeys. No acute withdrawal sign was observed in the vehicle treated monkeys, but in the 7-day withdrawal observation in these monkeys such withdrawal signs as apprehension, hyperirritability, tremor, muscle rigidity, and impaired motor activity were observed with grand mal convulsion on the 3rd day of withdrawal in 1 monkey. The mean withdrawal scores at 30 minutes after administration of Ro15-1788 or vehicle were evidently higher in the Ro15-1788 group than in the control group (Fig.2).

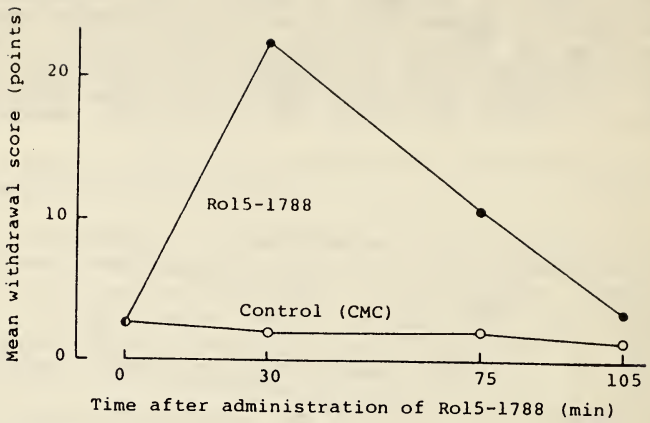

FIGURE 2 Ro15-1788 (●) and control (CMC) (○) were administered to respective 4 and 2 diazepam-dependent monkeys 2.5 hours after the last diazepam dose. The antagonist precipitated the diazepam withdrawal signs.

Experiment 4. Influence of Pentobarbital-Na Pretreatment on the Effects of Ro15-1788 in Diazepam-Dependent Monkeys

Precipitation tests of withdrawal signs by Ro15-1788 were conducted following pretreatment with pentobarbital-Na or saline in the 10th and 14th weeks of diazepam administration. In the saline-pretreated group the withdrawal signs similar to those observed in Experiment 3 were observed in both tests with one case of grand mal convulsion in the 10th week test. However, in the pentobarbital-Na pretreated group such signs as restlessness, muscle rigidity, and impaired motor activity were not manifested. Tremor was observed in most cases with the severity similar to that of the saline-pretreated group, and also vomiting and defecation were observed in 1 monkey each. The mean withdrawal scores of the pentobarbital-Na pretreated group were much lower than that of the control group at 0.5 and 1 hour after Ro15-1788 administration (Fig.3).

DISCUSSION

In the above experiments it has been demonstrated that the physical dependence-producing properties of barbital are not antagonized by Ro15-1788 but substituted by diazepam, that the physical dependence-producing properties of diazepam are antagonized by Ro15-1788 and also substituted by pentobarbital,

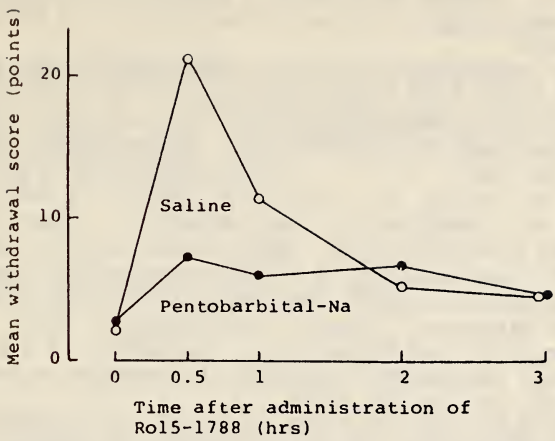

FIGURE 3 Monkeys physically dependent on diazepam were pretreated with pentobarbital-Na (●) or saline (○) 2.5 hours after the last dose of diazepam in 2 monkeys each, and 5 minutes later, Rol5-1788 was administered to all monkeys. The precipitated diazepam withdrawal signs in the pentobarbital-pretreated group were less severe than those of the saline-pretreated group. Four weeks later the test was conducted again by crossing over the animals for pentobarbital-Na and saline. The graph represents the mean withdrawal scores of the 2 tests (average of 4 monkeys each).

and that the cross physical dependence properties of diazepam to barbital are antagonized by the antagonist, but that of pentobarbital to diazepam does not appear to be antagonized by the antagonist. Thus, it became clear that the physical dependence-producing properties of both drugs do not differ from the other CNS effects in terms of antagonism by the benzodiazepine antagonist. These results indicate that the benzodiazepine receptors are involved in developing physical dependence on diazepam but not on barbital. Based on the fact that the cross physical dependence is observable between the barbiturates and diazepam, the sites responsible for developing physical dependence on these drugs are assumed to be same. Therefore, it is concluded that the sites may be located at higher parts of the CNS than the receptor sites.

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Quantitative Determination of LAAM and Its Metabolites in Human Biofluids

K. Verebey; A. Depace; and S. J. Mulé

ℓ-α-Acetylmethadol (LAAM) is currently an investigational new drug awaiting approval by the FDA for general use. Alternative drug therapy of opiate dependence with LAAM is very attractive for two main reasons. First, take-home medication is not needed due to its long-time action; thus diversion for illicit use would be greatly limited. Secondly, LAAM has a smooth therapeutic action eliminating the daily "highs" and "lows" observed with methadone. Active metabolite formation is responsible for the extended pharmacological action of LAAM as contrasted with methadone which forms only inactive metabolites. Because LAAM action depends on biotransformation to noracetylmethadol (NAM) and dinoracetylmethadol (DNAM), individual variation in drug metabolism and disposition will significantly influence the outcome of LAAM maintenance therapy.

The analysis of LAAM in biofluids reported in previous studies was performed by thin layer chromatography (Henderson et al. 1977; Misra et al. 1975; Campos-Flor and Inturrisi, 1977) by gas-liquid chromatography (Kaiko et al. 1975; Tse and Welling 1977; Billings et al. 1973; Lau and Henderson, 1976) by GC-MS (Sullivan et al. 1973; Jennison et al 1979) and by high-pressure liquid chromatography (Kiang et al. 1981). Most of these methods were sufficient for research purposes but too complicated for routine analysis. For this reason a method was developed in our laboratory with as few steps as possible.

METHOD OF EXTRACTION

The following solutions were added to 15 ml siliconized conical centrifuge tubes: SKF 525-A, 150 ng (the internal standard), 0.5 ml H_2O, 0.5 ml serum from a subject on LAAM maintenance and 100 ml of 50% NaOH. The tubes were mixed on a Vortex mixer and placed in a heating block at 75°C for 15 minutes. Heating and the alkaline environment converts LAAM metabolites into amides. This step was used to increase extractability of the polar metabolites NAM and DNAM. After removal from the heating block the samples were allowed to cool and 5.0 ml of n-butyl chloride was added. The samples were shaken for 10 minutes on an automatic shaker and cen-

trifuged for 5 minutes at 2000 RPM. The upper layer (n-butyl chloride) was transferred into clean test tubes and evaporated to dryness. After reconstitution with 25 µl of ethyl acetate, 5 µl aliquots were injected on to the capillary column.

GAS CHROMATOGRAPHY

A Hewlett Packard 5880A gas chromatograph was used with Nitrogen detector. The column was a 25 m, 0.2 mm diameter, wall coated OV-1 open tubular column (WCOT), made of fused flexible silica. The mode of operation was splitless injection and cold trapping with the split flow of 20 ml/min. The injector and detector temperatures were: initially 190° for 30 seconds, then the temperature was increased to a final value of 260° with a program rate of 30°/minute. The carrier gas helium was flowing at 0.5 ml/min through the column, the hydrogen at the detector was flowing at 3 ml/min and the air at 90 ml/min.

The retention times of LAAM, NAM amide and DNAM amide were 5.59 min, 10.10 min, 9.13 min respectively; SKF 525A had a retention time of 7.16 min. Blank serum extracts had no interfering peaks at the zones occupied by the compounds of interest.

Quantitation was performed by known standards of 5,10,20,50 and 100 ng added to 0.5 ml of blank serum with 150 ng of SKF-525A. The standards were extracted according to the method described for the unknown samples and analysed by gas liquid chromatography. The standard curve was linear up to 800 ng/ml which was the highest concentration tested.

The nitrogen detector's absolute sensitivity for LAAM, NAM and DNAM is 0.1 ng. However, after extraction from biological fluids 5 ng/ml can be comfortably quantitated. The limit of detection is approximately 1 ng/ml. Intra-run reproducibility (n=12) as measured by the coefficient of variation for LAAM, NAM and DNAM was 4.1, 4.7, and 6.1% respectively, indicating excellent dependability of the method.

The advantages of this method are: 1) speed, due to the single extraction step; 2) increased recovery of NAM and DNAM, due to the decreased polarity of the amides; 3) greater stability of the LAAM metabolites, due to their conversion to the amide configuration; 4) better chromatographic separation and quantitation because the area where the peaks migrate is free of interfering substances; 5) low sample volume helps to reduce the amount of blood needed for analysis, and 6) all three of the major pharmacologically active substances can be measured simultaneously.

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The Khat Alkaloid (-)Cathinone Acts Like Amphetamine on Physiological Catecholamine Stores

Peter Kalix

In certain areas of East Africa and the Arab Peninsula, fresh leaves of the khat bush are widely used as a stimulant. This material is now known to contain the alkaloid (-)cathinone, a substance that has been shown to produce amphetamine-like behavioral effects. The experiments described below were carried out in order to compare the effects of (-)cathinone and (+)amphetamine at the cellular level.

When the effect of (-)cathinone on the efflux of radioactivity from rabbit striatal slices prelabelled with ^{3}H-dopamine was examined, it was observed that low concentrations of the alkaloid enhanced the release of label in a dose-dependent manner. Furthermore, (-)cathinone was capable of sustaining an enhancement of a release induced by (+)amphetamine. Preperfusion of the tissue with cocaine, a substance that prevents the induction of release by (+)amphetamine, inhibited the efflux increase caused by (+)cathinone. In other experiments with dopamine-prelabelled tissue, the alkaloid was also found to cause release from the nucleus accumbens, a brain region that is essential for amphetamine hypermotility. These observations suggest that (-)cathinone is a CNS stimulant with a mechanism of action analogous to that of amphetamine.

Since consumption of khat is associated with sympathomimetic side effects, experiments were performed to determine whether the releasing action of (-)cathinone observed in the CNS also occurs in peripheral tissues. When slices of rabbit atria that had been prelabelled with ^{3}H-norepinephrine were superfused with solutions of either (-)cathinone or (+)amphetamine, a rapid increase of the efflux of radioactivity was observed. In tissue from reserpinized animals the releasing effect of (-)cathinone, as well as of (+)amphetamine, was characterized by rapid development of tachyphylaxis.

In summary, it was shown that (-)cathinone has an amphetamine-like releasing effect both at central dopaminergic synapses and at peripheral norepinephrine storage sites.

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Inpatient Heroin Withdrawal With Clonidine

Hans Schanda; Otto Presslich; and Peter Hermann

Experimental (Tseng et al., 1975) and clinical (Gold et al., 1980; Washton et al., 1980) studies pointed to the efficacy of clonidine for the treatment of heroin withdrawal. We have been using clonidine 1980 for the treatment of acute withdrawal syndromes in heroin addicts and attempted from the first to develop a clinically useful strategy for inpatient treatment.

METHODS AND POPULATION

Fifty patients (32 men, 18 women, mean age 23.7 years) entered the study. They were all pure heroin addicts (mean duration of opiate abuse 3.5 years). Admission to the program has to be voluntary. A contract was made for a minimum stay of 10 days on the unit (if necessary), with no visitors. Spot-checks of urine were done. Six patients arrived in a state of severe withdrawal (Kielholz stage two with perspiration, tearing, rhinorrhea, mydriasis, severe joint and muscle pains) on the ward. They got a single dose of 0.15 mg clonidine slowly i.v. Thereafter all further medication was administered orally on an "as needed" basis. Clonidine 0.075 mg (1 tablet = 0.15 mg) was given, when withdrawal symptoms corresponded to Kielholz stage 1 (1972), and could be repeated hourly. Our pre-study experience was that clonidine is ineffective against insomnia. So we offered doxepine 100 mg p.r.n. sleep throughout the hospital stay; for the first four nights, this could be augmented by nitrazepam 10 mg if required. Stages of withdrawal were classified clinical according to Keilholz et al., (1972). No rating scales were used. Liver function was performed routinely at least twice during hospitalization. Blood pressure and pulse frequency (supine) were taken three times a day throughout.

RESULTS AND DISCUSSION

Nine patients dropped out in the second or third day of withdrawal,

five because of treatment failure, four because of non-cooperation not due to non-response. Of the remaining 41 probands who completed the study mean length of required hospitalization was 7.78 days (range = 4 to 19 days, = 2.88). Clonidine was never required beyond 7 days (mean 5.1 days, = 1.26) (table 1).

TABLE 1

	Clonidine required until						
day	2	3	4	5	6	7	$\bar{x}$ = 5.098 days
n							(= 1.261)
patients	2	2	9	12	10	6	

The clonidine doses required (table 2) approximate the rapid detoxification schedule of 0.2 to 0.9 mg clonidine (daily average 0.5 mg), proposed by Washton, et al., (1980).

TABLE 2

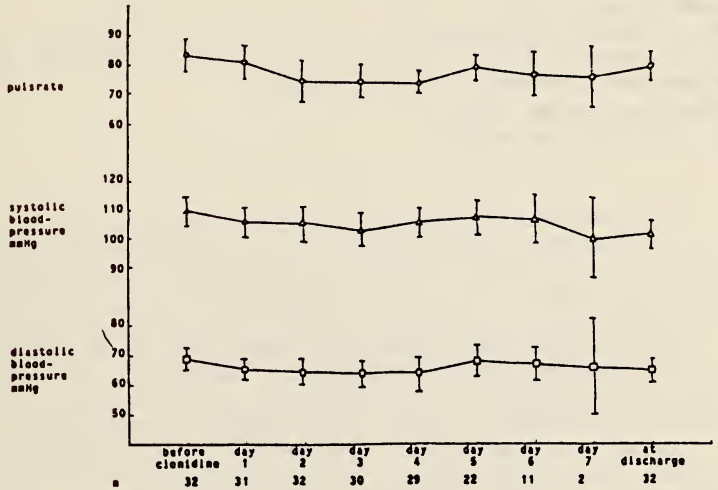
Daily required clonidine-doses in mg

day	subjects n	mean	min	max	
1	39	0.33	0		
			.075	1.35	0.24
2	41	0.468	0.075	1,65	0.298
3	39	0			
		.365	0.075	0.75	0.244
4	37	0.275	0.075	0.75	0.165
5	28	0.225	0.075	0.525	0.132
6	16	0.154	0.075	0.3	0.064
7	6	0.112	0.075	0.15	0.041

Nine of our 41 patients complained of symptoms of orthostatic hypotension, and were given a small dosage of a peripheral vasoconstrictor (norfenefrine) as needed. Reason for this orthostatic hypotension could of course be higher clonidine doses. But t-test for independent samples showed no significant differences in clonidine doses with or without a peripheral vasoconstrictor. There was also no significant difference between the two groups in the supine blood pressure before the first administration of norfenefrine. No significant changes in blood pressure and heart rate were seen in the 32 patients without vasoconstrictor (table 3), which does not correspond with the results of Charney, et al., (1981) and Gold, et al., (1980), who reported decrease of blood-pressure under clonidine. Maybe this is due to the use of doxepine (as sleep-medication on an "as needed" basis) which blocks the peripheral antihypertensive effect of clonidine (uptake into peripheral adrenergic neurons) (Briant, et al., 1973).

Our observation and the reports of the patients show that muscle and joint pains, muscle twitching and tremors, perspiration, psychomotor agitation, and occasionally, anxiety attacks are influenced by clonidine; gastro-intestinal disturbances (vomiting, diarrhea) and especially insomnia are unaffected by clonidine. As a consequence of this all subjects requested sleep medication at one time or other (100 mg doxepine; for the first four 4 nights 10 mg nitrazepam). Tenacious insomnia responds well to doxepine. Further antidepressants seem to be effective against the depression and anhedonia, which often follow opiate withdrawal.

FIGURE 1



Mean supine heart rate and blood pressure (with 5% confidence-intervals) during the seven clonidine days

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Withdrawal From Nocotine Dependence Using Mecamylamine: Comparison of Three-Week and Six-Week Dosage Schedules

Forest S. Tennant, Jr., and Anita L. Tarver

ABSTRACT

Mecamylamine (MCL) has been shown to extinguish nicotine dependence in animals and produce smoking cessation in some humans. This study was done to determine if MCL may be more effective and have fewer side-effects when administered at low dosages over a six-week period than at high dosages given over a three-week period. Subjects in the high-dose, three-week group demonstrated significantly more reduction of nicotine intake as evidenced by self-report and presence of nicotine in urine although side-effects were more pronounced. Although MCL's numerous side-effects should limit its clinical use to recalcitrant smokers who have failed other types of treatment, its nicotine antagonist property indicates it can be an effective agent to withdraw some persons from nicotine dependence.

INTRODUCTION

The ganglionic blocker, mecamylamine (MCL), has been shown to extinguish nicotine dependence in rats and monkeys.[1,2] In a preliminary clinical evaluation, we found that MCL was effective in withdrawing approximately 50% of recalcitrant nicotine-dependent persons when administered over a three-week period.[3] MCL was initially administered in a dose of 5 to 10 mg. per day and progressively raised over a period of ten days, until the subject experienced nicotine blockage or toxic effects. These high dosages over a short period of time, however, resulted in numerous side-effects. Reported here is a comparison of MCL given at low dosages over a six-week period with high dosages given over a three-week period to determine if the longer treatment period at low dosages may be effective and have fewer side-effects.

METHODS

Nicotine-dependent volunteers who met the following criteria were selected: smoked at least 20 (one pack) cigarettes per day; had not been nicotine abstinent for more than one day for at least one

year; no current history of hypertension, pregnancy, cardiovascular disease, prostate enlargement, glaucoma, or self-reported dependence upon alcohol or other drugs. Subjects did not take any prescription medication. Subjects also had to have the perception that they were "addicted" to nicotine. Eighteen (18) persons entered the three-week and fourteen (14) entered the six-week dosage regimens. Following informed consent, subjects underwent physical examination, blood pressure recording, and urine analysis for the qualitative presence of nicotine.[4]

Subjects in both groups attended the clinic daily for the first five days and then two or three times per week for the period of MCL administration. Dosage schedules for both groups are listed in Table One. Blocking dosage was achieved when the subject stated he/she could not perceive any nicotine effect. Whenever there was significant side-effect(s), MCL dosage was either reduced or held constant. Once a subject stopped smoking, they were allowed to voluntarily continue MCL administration throughout the duration of the assigned study period of three or six weeks.

During each clinic visit, the subject was examined for evidence of sedation, tremor, and motor impairment, and blood pressure was recorded in the sitting and standing positions. A daily check list of 24 side-effects was assessed, and the list included abdominal cramps, blurred vision, constipation, dizziness, drowsiness, dry mouth, dysphoria, headache, irritability, lethargy, palpitation, photophobia, tremor, urinary hesitancy, urinary retention, and weakness. Subjects were specifically asked on each day of attendance if MCL blocked the effects of nicotine; if it "works"; helps reduce nicotine craving, and if they wanted to continue MCL. Each subject kept a diary of the time of day and number of cigarettes smoked. A urine sample was submitted by subjects every day of attendance to be analyzed for the presence of nicotine.[4]

RESULTS

Both groups had similar demographic and nicotine use characteristics (Table Two). Ages ranged from 22 to 61 years. Subjects had smoked from 7 to 49 years and, at the time of admission to the study, smoked 20 to 80 cigarettes per day. The majority had relapsed following attendance at anti-smoking programs. A number of side effects were experienced by both groups of subjects (Table Three). The high-dose, three-week group had significantly more abdominal cramps, constipation, and urinary retention, while the low-dose, six-week group had more headaches. Side-effects were severe enough to cause almost one-half of subjects in both groups to drop out of the study. There was no drop in systolic or diastolic blood pressure in any subject greater than 15 mm Hg.

Although slightly higher percentage of three-week subjects (6; 33.3% compared to 3; 21.4%) reported they stopped smoking, the difference was not significantly different(PNS). A significant number of three-week compared to six-week subjects, however, reduced cigarette intake to less than five per day and converted

their urine from nicotine positive to negative on at least one urine test (Table Four). The majority of subjects in the three-week group perceived MCL to block nicotine and reduce nicotine craving, while only about half the six-week group felt this way.

Four of the six (66.6%) subjects in the three-week group, and the three in the six-week group who reported total cessation of smoking did so at a dose of 2.5 mg. QID (10 mg. in a 24-hour period). Two subjects in the three-week group stopped at dosages of 40 and 50 mg. per day. Slightly more subjects in the six-week group dropped out of treatment during the first week (33.7% compared to 10.6%; PNS). In addition, the mean retention time of 12.6 days in the six-week group was not significantly greater than the 9.3 days observed in the three-week group (PNS).

Two subjects in the three-week, and one in the six-week group desired to take MCL past the allotted time periods of the study. Three of the six (50.0%) subjects in the three-week group and one of the three subjects (33.3%) in the six-week group who reported total cessation of smoking had resumed smoking within 30 days following discontinuation of MCL.

DISCUSSION

This study was done to determine if low dosages of MCL given over several weeks might be more effective and have fewer side-effects than high dosages administered over a three-week period. Side-effects of MCL are particularly prominent in high dosages and they produce a high drop-out rate.[3] We found, however, that almost as many subjects dropped out of the six-week, low-dosage group due to side-effects. In addition, the low-dosage, six-week group had fewer persons (21.4% versus 33.3%) report total smoking cessation, although this was not a statistically significant difference. The three-week group did have significantly more persons reduce their cigarette intake to less than five per day and convert their urine from nicotine positive to negative.

Better results in the three-week group appeared to be due to progressive raising of the MCL dose to achieve nicotine blockade in the first week of treatment. Subjects in the high-dose group compared to the low-dose group tended to perceive that MCL was more effective in blocking nicotine and helping them reduce its intake. Apparently the achievement of almost total nicotine blockade with MCL is necessary to best retain patients in treatment and promote nicotine abstinence.

This study was not blind to either investigators or subjects, so data may be biased. Despite the open nature of this study, nicotine abstinence rates were not especially impressive, although the subjects selected for study were chronic, recalcitrant smokers. The majority had previously failed formal anti-smoking programs. In addition, MCL's numerous side-effects should limit its use to smokers who have failed other forms of nicotine dependence treatment. MCL does represent a new concept in treatment of drug dep-

endence.[4,5] The antagonists disulfiram and naltrexone are currently used as maintenance agents to prevent relapse to alcohol or opioid dependence. As a nicotine antagonist, MCL's best use appears to be that of a withdrawal agent, although some subjects who tolerated it well requested long-term maintenance.

TABLE ONE

DOSAGE SCHEDULES UTILIZED

	Three-Week Group N=18	Six-Week Group N=14
Day One	2.5 mg. BID	2.5 mg. BID
Day Two	2.5 mg. TID or QID	2.5 mg. TID
Days Three to Seven	Raised progressively to Blocking Dose*	2.5 mg. QID
Week Two	Maintained at Blocking Dose	2.5 mg. or 5.0 mg. QID
Week Three	"	"
Week Four	NA	"
Week Five	"	"
Week Six	"	"

* The maximum dosage given to any subject was 50 mg. in a 24 hour period.

TABLE TWO

CHARACTERISTICS OF SUBJECTS

	Three-Week Group N=18	Six-Week Group N=14	Stat Sig.
Males	9 (50.0%)	6 (42.9%)	PNS
Females	9 (50.0%)	8 (57.1%)	PNS
Mean Age (Yrs.)	37.2	38.1	PNS

Mean Use of Nicotine (Yrs.)	24.6	21.9	PNS
Mean No. Cigarettes Used Per Day	41.9	40.6	PNS
No. Who Perceive "Addiction" to Nicotine	18 (100%)	14 (100%)	PNS
No. Who Awake at Night to Smoke	9 (50.0%)	8 (57.1%)	PNS
No. Who Had Attended a Formal Anti-Smoking Program	11 (78.5%)	9 (64.2%)	PNS

TABLE THREE

SIDE-EFFECTS EXPERIENCED BY SUBJECTS

Side-Effect	Three-Week Group N=18	Six-Week Group N=14	Stat Sig.
Abdominal Cramps	10 (55.5%)	3 (21.4%)	$P < .05$
Blurred Vision	3 (16.6%)	2 (14.3%)	PNS
Constipation	13 (72.2%)	5 (35.7%)	$P < .05$
Dizziness	7 (38.8%)	5 (35.7%)	PNS
Drowsiness	8 (44.9%)	7 (50.0%)	PNS
Dry Mouth	13 (72.2%)	9 (64.3%)	PNS
Dysphoria	1 (5.5%)	1 (7.1%)	PNS
Headache	2 (11.1%)	6 (42.8%)	$P < .05$
Irritable	7 (38.8%)	4 (28.5%)	PNS
Lethargy	3 (16.6%)	3 (21.4%)	PNS
Palpitations	1 (5.5%)	2 (14.3%)	PNS
Photophobia	0 (0 %)	1 (7.1%)	PNS
Tremor	1 (5.5%)	1 (7.1%)	PNS
Urinary Hesitancy	4 (22.2%)	0 (0 %)	$P < .05$
Weakness	5 (27.8%)	7 (50.0%)	PNS

TABLE FOUR

RESULTS AND OUTCOMES

	Three-Week Group N=18	Six-Week Group N=14	Stat Sig.
No. who reported smoking cessation	6 (33.3%)	3 (21.4%)	PNS
No. who reported decrease in smoking to 5 or fewer cigarettes per day	12 (66.6%)	2 (21.4%)	$P < .05$
No. who converted from nicotine positive to negative on one test	13 (72.2%)	4 (28.5%)	$P < .05$
No. dropouts	10 (55.6%)	7 (50.0%)	PNS
No. who dropped out due to side-effects*	9 (50.0%)	6 (42.8%)	PNS
No. who dropped out due to non-effectiveness	1 (5.5%)	1 (7.1%)	PNS
No. who dropped out in first week of treatment	3 (16.6%)	5 (25.7%)	PNS
No. who perceived MCL blocks nicotine effects	16 (88.9%)	7 (50.0%)	$P < .05$
No. who perceived MCL to reduce nicotine craving	16 (88.9%)	6 (42.9%)	$P < .05$

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Biological Evaluation of Compounds for Their Physical Dependence Potential and Abuse Liability. VIII. Drug Testing Program of The Committee on Problems of Drug Dependence, Inc. (1984)

Arthur E. Jacobson

The program of the Committee on Problems of Drug Dependence (CPDD) on the biological evaluation of compounds for their physical dependence potential and their abuse liability has, up to the past few years, primarily concerned opioids. This testing program uses procedures which are capable of determining the biochemical and pharmacological activity of opioids and differentiating opioid agonists, agonist-antagonists, and the opioid antagonists. About two years ago the CPDD began to investigate the methodology necessary for the determination of the abuse liability of pharmacologically different classes of compounds, the stimulants and depressants. We have now completed the initial assessment of methodology and have enlisted, under CPDD auspices, several laboratories to aid in the abuse liability determination of new stimulants and depressants. During the coming year the program will study a number of stimulants which are scheduled for examination by the World Health Organization in 1985.

LABORATORIES UNDER CPDD AUSPICES CONCERNED WITH OPIOIDS

Three laboratories are involved in the work on opioids. The initial testing, in mice, for antinociceptive activity and for the determination of a starting dose for further work in the rhesus monkey, is done in the Medicinal Chemistry Section, LC, NIADDK, NIH (Dr. A. E. Jacobson, with the technical assistance of M. Mattson). The compounds which I receive from various sources are distributed to the two other groups involved in the evaluation. These groups are those at the Medical College of Virginia, Department of Pharmacology (Drs. L. S. Harris, M. D. Aceto, E. L. May, R. L. Balster and B. L. Slifer, with the technical assistance of F. T. Grove, R. F. Jones, S. M. Tucker, W. D. Rodes and S. R. Phillips), and at the University of Michigan Medical School, Department of Pharmacology (Drs. J. H. Woods, G. D. Winger, F. Medzihradsky, C. B. Smith and D. Gemerk). Evaluation of the compounds has been described heretofore (Jacobson 1981). Modifications of these procedures are described below.

MODIFICATIONS IN PROCEDURES FOR EVALUATION OF OPIOIDS

The individual Annual Reports from UM and MCV will, for the second consecutive year, be combined under a single code number and structure. The assigned code number will be the NIH number given to the compound at NIH. A new cumulative dosing procedure will be used at UM in their monkey studies. This will enable them to obtain information on the physical dependence potential of compounds more rapidly. Single doses will be used, when necessary, retrospectively on compounds of interest. Further, at UM, the in vitro work using rat cerebrum membranes will be carried out in the presence of 150nM NaCl only. These data can be correlated with the data previously obtained at UM through use of their +Na/-Na ratios. That is, the binding of compounds to the rat cerebrum membranes in the absence of sodium can be obtained by dividing the value noted for the EC50 in the presence of sodium by the ratio of (+)Na/(-)Na (noted in parentheses in the Tables in my previous reports (Jacobson 1984) and in those from UM, or in the combined Annual Report (Woods et al. 1984)). It should be noted that the shift observed with narcotic antagonists in the presence of sodium may only partially be due to their opioid antagonist character. There is now evidence (Loew 1984) that opioid receptors other than mu or delta are involved in the binding of ligands when sodium is added. Lastly, the electrically stimulated guinea pig ileum assay has been discontinued to expedite the evaluation, and because the ileum has not been found to be as predictive as the mouse vas deferens assay.

THE ORIGIN AND TYPES OF "OPIOIDS" EXAMINED

Relatively few compounds were sent for evaluation from pharmaceutical industry (13% total, 8% from US industry). An additional 12% were solicited from US industry by the CPDD; these were the antihistamines discussed below. US universities submitted 34% of the compounds evaluated, and foreign universities submitted 7%. The NIH submitted 22% and CPDD requested 7% of the compounds, the latter serving as reference samples. The remaining 5% of the compounds came from foreign industry, in collaboration with a US university study. A relatively large number of compounds were released for publication; there are 61 compounds listed in the MCV Annual Report and 50 compounds listed in the UM Report. Consolidation in the NIDA monograph will result in a combined report on a somewhat lower total number.

The tables 1-7 which follow contain a summary of the work completed on the released compounds; structurally similar compounds are grouped together. Work was done with 4,5-epoxymorphinans (tables 1 and 2), morphinans (table 3), benzomorphans (table 4), and phenylmorphans (table 5). The antihistamines are included among the miscellaneous compounds in tables 6 and 7. It is of particular interest to note endoethenooripavine-like compounds with peptide moieties in table 2.

One of them, NIH 9835, has one of the highest affinities for the opioid receptors in rat cerebrum membranes ever observed. Its relatively mediocre antinociceptive activity (morphine-like) may have been caused by the inherent in vivo instability of peptides with all L-amino acids.

EVALUATION OF STIMULANTS AND DEPRESSANTS

This evaluation has been undertaken by Drs. J. Brady, N. Ator, R. Griffiths, and R. J. Lamb of the Johns Hopkins University Medical School, Drs. C. Johanson and C. R. Schuster of the University of Chicago Medical School, Drs. R. Glennon, L. Harris, M. Aceto, E.L. May and G.A. Patrick of the Medical College of Virginia, and by Drs. C. Gorodetzky, E. Cone, M.E. Risner, H. E. Shannon and D. B. Vaupel of the Addiction Research Center of the National Institute on Drug Abuse, ADAMHA. Over the past two years a number of depressants and stimulants have been examined and the results have been reported at the CPDD Annual Meeting and to the Drug Testing Program Committee of the CPDD. A complete report is being prepared for the CPDD and for distribution to the submitters of the compounds.

The evaluation procedure is initiated by myself at NIH, where a CPDD number is assigned to the compound. Dr. Cone (ARC) then determines the solubility of the compounds in the required solvents. He also runs TLC and IR spectra for compliance with the Good Laboratories Practice Regulations of the FDA. The compound is initially evaluated for potency by an inverted platform assay and in activity cage studies in rodents (Dr. L. Harris et al., MCV) and, if the compound is in the benzodiazepine class, their affinity to the benzodiazepine receptors in rat brain homogenate is determined (Dr. Jacobson and M. Mattson, NIH). The study is continued in drug discrimination and self-injection paradigms in monkeys and in drug discrimination in pigeons (Drs. Johanson and Schuster, Univ. of Chicago). Drug discrimination assays in baboons and, electively, self-injection, are done at the Johns Hopkins Univ. (Dr. Brady et al.). Dr. R. Glennon (MCV) will aid in the evaluation of stimulants, using drug discrimination assays in rodents.

ANTIHISTAMINES EVALUATED

The ten antihistamines which have been evaluated this year are listed in tables 6 and 7. These are phenyltoloxamine, cyclizine, hydroxyzine, promethazine, tripelennamine, pyrilamine, diphenhydramine, chlorpheniramine, cimetidine, and flunixin. Reasonable correspondence between the results from MCV and UM was observed except for cyclizine, which will be reevaluated. Few of the compounds showed much antinociceptive activity nor had typical opioid patterns of action. Tripellenamine was the most potent of the antihistamines as an antinociceptive.

ABBREVIATIONS USED IN TABLES 1 - 7.

Antinociceptive assay (ED50, sc injection, mice) [Confidence limits are listed in MCV/UM report]: HP = hot plate; N = Nilsen; PPQ = phenylquinone; TF = tail flick; TFA = tail flick antagonism vs. morphine.

I = inactive, without a reasonable dose-response relationship, or insufficiently active for statistical analysis.

EC50 Determinations in vitro and ex vivo:

RBH (EC50 by displacement of 0.5nM ^{3}H-etorphine) = binding affinity, in the presence of 150mM NaCl, to rat cerebrum membrane preparations, in nM (parenthesized number is ratio of +Na/-Na). The EC50 of morphine, for comparison = 23.6 (1.69). NE = no effect. NOTE: The present EC50 data cannot be directly compared with those from my previous reports (Jacobson 1983, and previous years) since I formerly quoted -Na values. However, the previously stated numbers can be calculated for comparison with those which will be utilized this year and in the future (vide supra).

GPI = electrically stimulated guinea pig ileum EC50, rounded to one significant figure. E = x10 (parenthesized numbers are maximum percent inhibition at EC50); [bracketed letters: A = antagonized by 10-7M naltrexone; NA = not antagonized by naltrexone; NE = no inhibition of twitch]. NOTE: The GPI assay is being phased out of the normal routine. These data will not be obtained as part of the general assays. The VD assay will continue.

VD = electrically stimulated mouse vas deferens EC50 values, rounded to one significant figure. E = x10 (parenthesized numbers are maximum percent inhibition at EC50); [bracketed letters: A = antagonized by 10-7 M naltrexone; NA = not antagonized by naltrexone; NE = no inhibition of twitch; SA = slight antagonism by naltrexone].

Data From Monkey Colonies:

SDS = single dose suppression: NS = no suppression; CS = complete suppression; PS = partial suppression. (Parenthesized numbers = dose range studied, in mg/kg; if CS, then dose at which CS was observed is noted in the parentheses). Potency comparison with morphine [M] may be stated, in brackets.

NW = studies in non-withdrawn monkeys: PW = precipitated withdrawal at dose levels, in mg/kg, indicated in parentheses &/or comparison with naloxone [N], in brackets; NP = no precipitation; SP = slight precipitation.

Other Studies:

RI = rat infusion: NS = no suppression; CS = complete suppression; PS = partial suppression.

PPD = primary physical dependence.

SA = self-administration: NE = no effect; High = codeine-like; IN = intermediate between saline and codeine; SE = slight effect.

Normal monkeys: M-like = morphine-like effect.
DD = drug discrimination.

NOTE: The numbers used in the tables may be rounded. For precise values, and details of the procedures, see the MCV/UM report in these Proceedings.

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Loew, G.H., Stanford Research Institute, NICHD lecture, NIH, March 1984.

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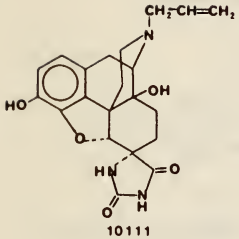
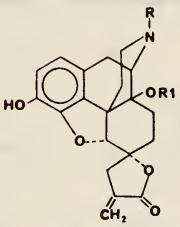
TABLE 1 - 4,5-EPOXYMORPHINANS[a]



10111



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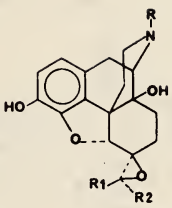
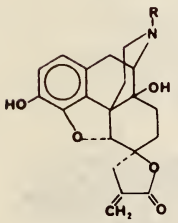
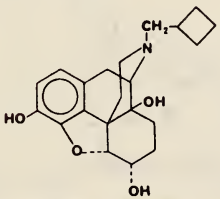
10069: R=CPM, R1=H
10070: R=Me, R1=COMe
10071: R=Me, R1=H



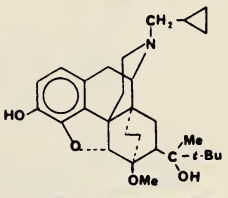
10147: R=CPM, R1=R2=H
10148: R=ALLYL, R1=R2=H
10163: R=Me, R1=R2=H
10311: R=CPM, R1=COOEt, R2=H



10149: R=CPM
10164: R=Me



10274: NALBUPHINE

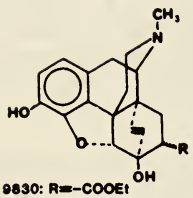


10276: BUPRENORPHINE

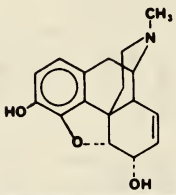
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	SDS	NW /OTHER
10068	4326		I		I	I	0.08	NS(0.003-0.05)	PW(0.0125)[1xN]
10069	4327		I		I	I	0.1	NS(0.006-0.1)	PW(0.4)[0.1xN]
10070	4328		4.1		2.0	8.5	I	NS(3-12)	
10071	4329		2.6		0.9	8.9	I	CS(16)[0.5xM]	
10111	4337		I		I	I	I		
10147	4341	10147	I		I	I	0.007	NS(0.1)	PW(0.003)[0.3xN]
10148	4342	10148	I		I	I	0.003	NS(0.1)	PW(0.03)[0.3xN]
10149	4343	10149	I		I	I	0.15	NS(0.1)	PW(0.3)[0.02xN]
10163	4352	10163	0.17		0.02	0.3	I	CS(1.0)[5xM]	
10164	4347		2.6		2.4	5.2		NS(2.5-10)	
10274	4385		13.0		~30	I	I	CS(10)	
10276	4387		0.04	0.04	0.016	0.14	1.0	PS(0.005,0.02)[b]	/RI -SM & PPD
10311	4394		I	I	I	I	0.3	NS(0.001-0.1)	PW[c]

a) See text for explanation of abbreviations.
b) No substitution occurred under 9 or 19 hour withdrawal, rather than 15 hour.
c) Much longer duration of action than naloxone.

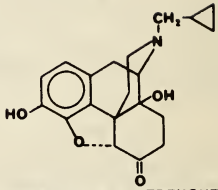
TABLE 2 - 4,5-EPOXYMORPHINANS (CONTINUED)[a]



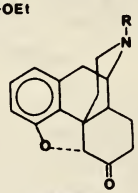
9830: R=-COOEt
9831: R=-COOEt
9833: R=-CO-L-Phe-L-Leu-OEt
9835: R=-CO-L-Gly-L-Phe-L-Leu-OEt



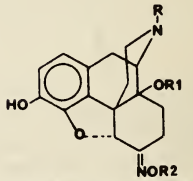
9929, 0001: MORPHINE



9930, 8503: NALTREXONE



9976: R=ALLYL

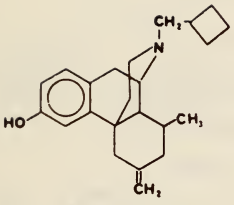


10002: R=ALLYL, R1=R2=H
10187: R=CPM, R1=H, R2=Me
10188: R=ALLYL, R1=H, R2=Me
10189: R=Me, R1=H, R2=Me

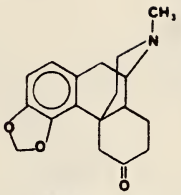
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW /OTHER
9830		1295	0.04					10 (0.55)		6E-8[A]		
9831		1296	0.35					27		1E-7[SA]		
9833		1297	0.83					0.58		1E-9[A]		
9835		1299	1.1					0.02		2E-8[NA]		
9929	4260	1311	1.0	1.5				51		4E-7[A]		
9930	4002	1312	I					0.97(0.37)	2E-9[A] 2E-4[A]	5E-9[SA]		
9976	4297	1362	6.4	8.3				265(0.84)		3E-7[A]		
10002	4309	1371	I	I				610		2E-6[NA]		
10187	4376	10187	I	I	3.9	I	0.08					PW(0.01-0.056) [0.5xN]
10188	4377	10188	I	I	I	I	1.9					PW(0.3)[0.1xN]
10189	4378	10189	0.22		0.02	0.08	I				CS(0.1)[100xM]	

a) See text for explanation of abbreviations.

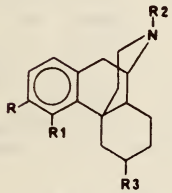
TABLE 3 - MORPHINANS [a]



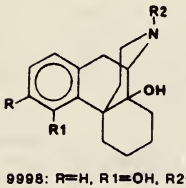
9736



9842: (-)



9974: R=H, R1=OH, R2=ALLYL, R3= =O
9989: R=R1=R2=H, R3=Me
10010: R=R1=H, R2=ALLYL, R3= =O
10016: R=R1=OMe, R2=ALLYL, R3= =O
10018: R=R1=OMe, R2=PHENETHYL, R3= =O

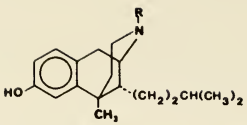


9998: R=H, R1=OH, R2=Me
10275: R=OH, R1=H, R2=CBM
BUTORPHANOL

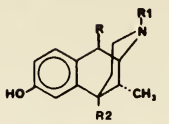
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW /OTHER
9736	4196	I	1.3									/PPD[b]
9842		1352	6.3					658(1.15)		1E-6[SA]		
9974	4295	1361	1.8	0.33				223(1.96)		7E-7[A]		
9989	4299	9989	2.3	2.5				375		3E-9[NA][c]		
9998		1369	0.93	1.7				115(1.06)	1E-6[A][d]			
10010	4316	1379	2.9	1.8				320		2E-7[A]		
10016	4318	1383	10.6					78		1E-7[NA]		
10018		1385	0.14	0.02				1.75		6E-8[A]		
10275	4386		0.8	0.09	I	I	I				NS(0.05-0.5)	

a) See text for explanation of abbreviations.
b) Inconclusive; terminated due to development of skin ulcers.
c) Shift to left in presence of naltrexone, with decreased maximum effect.
d) Only slight (<10%) inhibition of twitch.

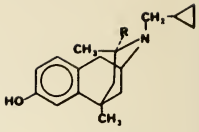
TABLE 4 - BENZOMORPHANS[a]



9450: R=Me
10156: R=n-AMYL
10157: R=PHENETHYL
10158: R=n-PROPYL
10159: R=ALLYL
10160: R=CPM
10172: R=ETHYL
10173: R=n-BUTYL



9938: R=H, R1=$(CH_2)_2CH(Me)_2$, R2=CH_3
10165: R=O, R1=CPM, R2=Et (EKC)
10249: R=H, R1=CH_2-cyclopropyl, R2=CH_3

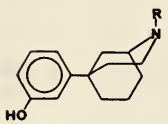


10142: R=H
10144: R=ALLYL

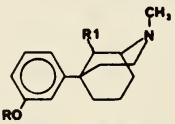
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW /OTHER
9450	4276	1305	14.1	19.7				62?(1.7)		2E-8[NA]		
9938	4269	1321	8.3		2.6	3.3	I	188(1.8)	1E-6[A]	7E-7[A]	NS(3-12)	
10142	4365		2.4		0.2	3.0	I					
10144	4366		3.7		7.0	I	I					
10156	4345		I		I	I	I				NS(4-16)	
10157	4342	10157	I		I	I	I				NS(5.6-10)	
10158	4346		I		7.0	I	14.8				NS(2.5-5)	NP(1.25-5)
10159	4350	10159	I		10.3	I	11.2				NS(1.7-10)	NP(1.7-5.6)
10160	4351	10160	I		14.4	I	5.5				NS(3-10)	
10165	4348	10165	0.09		0.04	0.4	I					/RI-PPD[b]
10172	4367	10172	I		I	I	I				NS(5.6-17)	
10173	4368	10173	I		27.3	I	I				NS(5.6-15)	
10249		10249	I								NS(1.-5.6)	

a) See text for explanation of abbreviations.
b) No physical dependence noted.

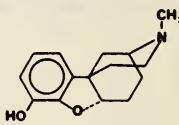
TABLE 5 - PHENYLMORPHANS[a]



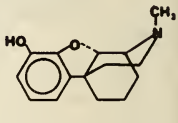
9882, 8508: (-)R=Me
9886: (-)R=n-AMYL
9887: (-)R=n-HEXYL
9888: (+)R=H
9889, 8509: (+)R=Me



9945: R=Me, R1=...Me
10021: R=COMe, R1=...OCOMe



10171

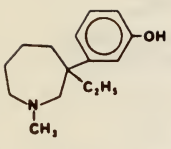


10224

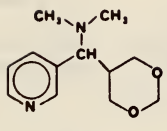
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	OTHER
9882 8508	4240 4231	1283 804	2.0									SA(iv)-IN
9886	4233	1285	I	I				155(0.3)		0.4E-9[NA]		
9887	4234	1286	I	I				27.8(0.24)		0.5E-9[NA]		
9888	4243	1287	I					263(1.1)	7E-7[A]	3E-6[A]		
9889 8509	4232	0.35										SA(iv)-IN
9945	4286	1327	I					>6000		>1E-4[NE]		
10021	4405	1388	2.0		1.0	7.3	I	4246(1.2)		3E-9[NA]	CS(5)	
10171	4369		I			I	I					
10224	4393		I		I	I	ca.30					

a) See text for explanation of abbreviations.

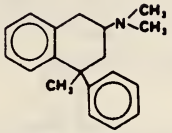
TABLE 6 - MISCELLANEOUS[a]



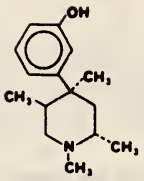
6683



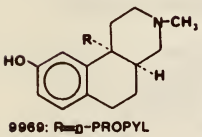
9344: (-)



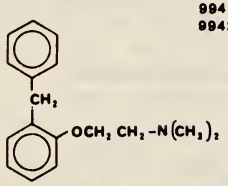
9941: (-)
9942: (+)



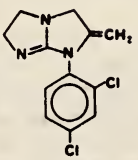
9922



9969: R=n-PROPYL
9970: R=Me



10121, 10197: PHENYLTOLOXAMINE

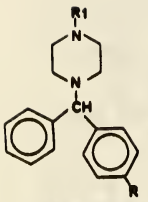


10146

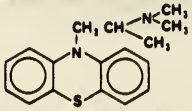
NIH#	MCV#	UM#	HP	N	PPQ	TF	TFA	RBH	GPI	VD	SDS	NW /OTHER
8683	4403		5.3		1.6	12.8	I				NS(0.2-3.2)	PW(0.2-6.4) [0.005xN]
9344	4104		4.9		6.4	17.9	I					/RI-PPD[b]
9922	4259	1320	2.4					141(1.67)		9E-9[SA][c] 8E-6[SA]		
9941	4283	1331	13.1					>6000		4E-9[SA]		
9942	4284	1332	I					>6000		4E-9[SA]		
9969		1346	9.0		1.5	8.8	I				CS(5.6)[0.5xN] CS(12)[0.25xN]	
9970	4292	1357	2.6		1.4	2.7	I	1354(0.93)	>3E-4	2E-7[SA]	PS(3-24)	
10121	4338	10121	40.5	I	1.3,2.8	I	I				PS(10-30	/RI-MS[d]
10197	4373		I	I	I	I	I				NS(5.6-30)	
10146	4339	10146	6.3	24.3	2.6	I	I				NS(3-6) NS(3-10)	

a) See text for explanation of abbreviations.
b) Less dependence than with morphine.
c) Biphasic action.
d) No substitution for morphine.

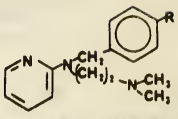
TABLE 7 - MISCELLANEOUS (CONTINUED)[a]



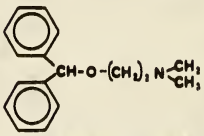
10169: R=H, R1=Me (CYCLIZINE)
10174: R=Cl, R1=$(CH_2)_2O(CH_2)_2OH$ (HYDROXYZINE)



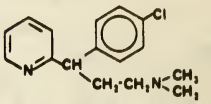
10170: PROMETHAZINE



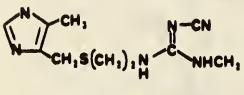
10186: R=H (TRIPELENNAMINE)
10248: R=OMe (PYRILAMINE)



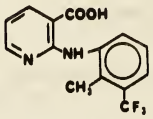
10175: DIPHENHYDRAMINE



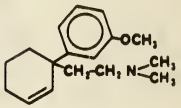
10215: CHLORPHENIRAMINE



10216: CIMETIDINE



10250: FLUNIXIN



10292: (±)
10293: (-)
10294: (+)

NIH#	MCV#	UM#	HP	N	PPJ	N'	TFA	RBH	GPI	VD	SDS	NW /OTHER
10169	4361	10169	I	23.9	7.4	I	I				NS(5-20) CS(10)[0.5xM]	
10170	4362	10170	I	I	1.7	I	4.7 I				NS(5.6-17) PS (5-20)	
10174	4363	10174	I		I	I	8.2 I				PS(4-30) NS(5.6-30)	
10175	4364	10175	I		5.6 14.8	I	I				NS(3.5-14) PS(5.6-30)	
10186	4375	10186	3.9		1.3 31.6	I	I				PS(3-10) NS(0.25-4)	SP(6-8)
10215	4380		I		I	I	I				NS(0.25-8)	
10216	4381		I		I	I	I				NS-PS(5-30)	
10248	4379		32.8	17.7	13.1 70.6	I	I				NS-PS(0.25-16)	
10250	4384		I		I	I	I				PS(20-40)	
10292	4396	10292	5.2		4.3	I	I	>6000		2E-7[SA]	NS(0.6-10)	
10293	4397	10293	4.3		3.0	I		1100		1E-7[NA]	NS(0.6-10)	
10294	4398	10294	6.0		1.8	I	I	>6000		7E-8[SA]	NS(0.6-5)	

a) See text for explanation of abbreviations.

Evaluation of New Compounds for Opioid Activity in Rhesus Monkey, Rat, and Mouse (1984)

James H. Woods; Gail D. Winger; Fedor Medzihradsky; Charles B. Smith; Debra Gmerek; and M. D. Aceto; L. S. Harris; E. L. May; R. L. Balster; and B. L. Slifer

Details of these techniques have been presented in the ANNUAL REPORT to the Committee in 1963 (Minutes of the 25th Meeting) by Deneau and Seevers (1963) and by Villarreal (1973).

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Medicinal Chemistry Section, NIADDK, National Institutes of Health, Bethesda, MD. The drugs, which come originally from pharmaceutical companies, universities, and government laboratories, are submitted to Dr. Jacobson, who performs the mouse hot-plate and Nilsen tests. [(Only Beta-funaltrexamine and dynorphin fragments and vasopressin, tested in the Medical College of Virginia, were not supplied by Dr. Jacobson.)] Values obtained in these tests for some representative opioid drugs are given in Table I.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information, and (4) a recommended starting dose. Only after the evaluation is complete and the report submitted back to Dr. Jacobson are the chemical structure and the mouse-analgesia data released to the evaluating laboratory.

DEPENDENCE EVALUATION IN RHESUS MONKEYS

The single-dose suppression test (SDS) determines the ability of a drug to suppress the signs of withdrawal in monkeys which have been made dependent by the chronic administration of morphine (3 mg/kg every six hours). Compounds suspected of having morphine-antagonist properties are tested for their ability to precipitate the withdrawal syndrome in nonwithdrawn (NW) morphine-dependent monkeys. Nondependent monkeys (Normals) are used to determine whether the acute effects of the test drug are reversible by nalorphine or naloxone. In a primary dependence study (PDS), non-dependent monkeys receive the test drug every six hours for 30 days to determine whether withdrawal signs will appear when

the animals are challenged with an antagonist or when drug administration is discontinued.

Modified procedures for the precipitated withdrawal (PPt-W) and single dose suppression (SDS) tests were reported by Aceto and co-workers (1977 and 1978). The PPt-W test was initiated by the injection of a test drug 2½ hours after an injection of morphine and the animals were observed for signs of withdrawal. The SDS test was started approximately 15 hours after the last dose of morphine at which time the animals were showing withdrawal signs. The onset and duration of action of the test drug were noted. In both tests, a vehicle control and an appropriate positive control (naloxone 0.05 mg/kg or morphine sulfate, 3.0 mg/kg) along with 3 different treatments (doses) of a test compound were randomly allocated to the 5 monkeys of a group. Occasionally 4 monkeys comprised a group and 2 doses of test compound were studied. Usually, 3 or 4 groups per compound were used. All drugs were given subcutaneously or (1 ml/kg) intravenously (1-2 ml) and the vehicle used is indicated for each compound. The observer was "blind" with regard to the treatment given. A minimum 2-week washout and recuperation period between tests was allowed. In the primary physical dependence (PPD) test, the animals of a group received the drug every 4-6 hr for 30-50 days. They were placed in abrupt withdrawal and challenged with naloxone periodically and were observed for signs of physical dependence.

TABLE 1

MOUSE ANALGESIA. Before submission to The University of Michigan, all compounds are evaluated for analgesic activity by Dr. Arthur E. Jacobson.[a-c] Shown below are comparative data (ED 50mg/kg) (95% Confidence Interval) from Hot Plate[d] and Nilsen[d] assays.

Compound NIH #	HOT PLATE (sc,mg/kg) (sc, umol/kg)	 (oral,mg/kg) (oral, umol/kg)	NILSEN (sc,mg/kg) (sc, umol/kg)	 (oral,mg/kg) (oral, umol/kg)
Morphine sulfate NIH 0001, 9929	0.98 (0.83-1.1) 2.9 (2.5-3.3)	6.3 (4.7-8.3) 18.9 (14.1-24.9)	1.3 (1.0-1.7) 3.9 (3.0-5.1)	8.3 (6.0-11.4) 24.9 (18.0-34.1)
Codeine phosphate NIH 0002	6.8 (4.5-10.2) 17.1 (11.3-25.7)	13.5 (9.7-18.7) 34.0 (24.4-47.1)	7.4 (4.9-11.0) 18.6 (12.3-27.7)	14.7 (9.2-23.3) 37.0 (23.2-58.7)
Levorphanol tartrate NIH 4590	0.2 (0.1-0.3) 0.5 (0.2-0.7)	- -	0.2 (0.16-0.3) 0.5 (0.4-0.7)	2.5 (1.7-3.7) 6.2 (4.2-9.1)
Meperidine·HCl NIH 5221	5.3 (4.0-7.1) 18.7 (14.1-25.0)	- -	- -	- -
(-)-Metazocine·1HBr NIH 7569	0.6 (0.5-0.9) 1.9 (1.4-2.8)	10.6 (8.0-14.1) 34.1 (25.7-45.3)	0.5 (0.3-0.7) 1.6 (1.0-2.3)	26.0 (21.0-33.0) 83.6 (67.5-106.1)

TABLE 1 Continued

Dihydromorphinone·HCl NIH 0123	0.19 (0.15-0.25) 0.6 (0.5-0.8)	0.9 (0.7-1.2) 2.8 (2.2-3.7)	0.2 (0.15-0.3) 0.6 (0.5-0.9)	1.8 (1.5-2.1) 5.6 (4.7-6.5)
Nalorphine·HCl NIH 2105	9.9 (5.7-17.1) 28.4 (16.4-49.1)	- -	23.0 (16.2-32.7) 66.1 (46.6-94.0)	- -
Cyclazocine NIH 7981	1.5 (1.1-2.1) 5.5 (4.1-7.7)	- -	0.1 (0.07-0.16) 0.4 (0.3-0.6)	- -
Pentazocine NIH 7958	9.3 (6.7-12.8) 32.6 (23.5-44.9)	- -	6.5 (4.4-8.8) 22.8 (15.4-30.9)	- -
Naltrexone·HCl NIH 8503	No dose response			
Naloxone·HCl NIH 7890	No dose response			

No antinociceptive activity in hot plate assay: Phenobarbital, amborbital, diazepam, meprobamate, mescaline, oxazepam, flurazepam.

Chloropromazine·HCl	1.1 (0.9-1.5) 3.2 (2.4-4.2)

a) Eddy and Leimbach (1953); b) Jacobson and May (1965); c) Atwell and Jacobson (1978) d) Perrine, Atwell, Tice, Jacobson and May (1972).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys was studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, directly observable changes in behavior were produced by the compound.

The schedule of intravenous drug delivery was a fixed-ratio 30; when a light above a lever was illuminated, the 30th response produced a five-second intravenous drug injection accompanied by another light that was illuminated during drug delivery. After each injection, a ten-minute timeout condition was in effect during which responses had no scheduled consequence and neither light was illuminated. Each of the two daily sessions consisted of 13 injections or 130 minutes, whichever occurred first. Other details of the procedure and initial findings with a variety of narcotics are given in previous reports (Woods, 1977; 1980).

Doses of the drugs are typically described in terms of moles/kg/injection (inj), to facilitate direct comparisons among drugs. Duplicate observations of codeine (7.5×10^{-7} mol/kg/inj; 0.32 mg/kg/inj) and of saline were obtained for each monkey. A saline substitution was conducted before and after the series of observations on a test drug; the control rates of codeine-reinforced responding were obtained by a random sampling of two sessions between the drug- substitution sessions. These data are represented in the following graphs with individual symbols for each of the monkeys; each symbol is the mean of duplicate observations for a given dose in each monkey. There are two additional types of averaged data presented. The closed circles indicate the averaged data for observations on the subset of monkeys used to study each drug under each of the experimental conditions. The open circles indicate the codeine and saline rates of responding of 20 monkeys studied under the same conditions. The brackets indicate ± 3 standard errors of the codeine mean, and ± 3 standard errors of the saline mean for the group of 20 monkeys. In all cases, the rates of responding given are those calculated during only the fixed-ratio portion of each session.

Intravenous self-administration studies, at MCV, were carried out as described previously (Slifer and Balster, 1983). Adult male rhesus monkeys were prepared with chronic intravenous catheters which were protected by a vest and restraining arm arrangement. They were trained to lever press under a fixed-ratio 10 schedule for intravenous cocaine hydrochloride during daily one-hour sessions. Injections were 1.0 ml delivered over 10 sec. When responding was stable, test solutions were substituted for four days. Between each substitution the subjects were returned to cocaine for at least three days. The vehicle for each test drug

(usually 0.9% saline) was also substituted for four days. The data from the last three days of each substitution was used in the data analyses. A dose was considered for function as a reinforcer in a particular subject if the mean for the three days exceeded the vehicle mean and the ranges did not overlap. Cocaine baseline injection rates were determined for each subject from the average of the three-day means preceding each dose substitution for each drug or drug pair tested.

RAT-INFUSION

The rat-infusion method was reported by Teiger (1974) and certain modifications were indicated as follows. Semi-restrained male Sprague-Dawley rats were medicated by continuous infusion through indwelling, intraperitoneal cannula for 6 days with the drugs. Rats were anesthetized and each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted in the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flowthrough, swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. Animals received 7 to 10 ml of solution every 24 hours.

In the substitution for morphine (SM) test, the animals first received morphine (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3-6). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of water. The animals were observed for changes in body weight and for behavioral-withdrawal signs for ½ hour at 6,24,48,72 and/or 96 hours after stopping the infusion of morphine.

In the primary physical dependence (PPD) study, the rats received test compound for 6 days and then were placed in abrupt withdrawal and observed as above.

MOUSE TESTS

Three mouse tests were used in the laboratory at the Medical College of Virginia to provide a preliminary estimate of the potency and profile of activity of each test compound. The tests were the tail-flick agonist (TF) and the morphine antagonist (TF vs M) tests and the phenylquinone (PPQ) test (Dewey et al., 1970; Dewey and Harris, 1971). Reference-standard data for these tests are shown in Table II. In addition, Dr. Jacobson provided us with estimated starting doses. These doses are based on results obtained from the mouse hot plate (HP) (Eddy and Leimbach, 1953; Jacobson and May, 1965; Atwell and Jacobson, 1978) and Nilsen (N) (Perrine et al., 1972) tests from his laboratory. Reference data for these tests are shown in Table I.

TABLE II

Comparative Data-ED50 mg/kg s.c. (95% C.L.) of Selected Standards in Three Mouse Agonist-Antagonist Tests

Drug	Tail-Flick Test	Tail-Flick Antagonism Test	Phenylquinone Test
Pentazocine	15% at 10.0	18 (12.4-26)	1.65 (1.0-2.5)
Cyclazocine	17% at 1.0[a]	0.03 (0.2-0.78)	0.011 (0.0046-0.03)
Nalorphine.HCL	None at 10.0	2.6 (0.69-9.75)	0.6 (0.25-1.44)
Naloxone·HCL	None at 10.0	0.035 (0.010-0.93)	No Activity
Naltrexone·HCL	None at 10.0	0.007 (0.002-0.02)	No Activity
Morphine Sulfate	5.8 (5.7-5.9)	- - -	0.23 (0.20-0.25)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but no further increase in reaction time was seen.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Details of the binding assay were described in the 1978 ANNUAL REPORT (Swain et al., 1978). Briefly, aliquots of a membrane preparation from rat cerebrum were incubated with ^{3}H-etorphine in the absence and presence of 150 mM NaCl, and in the presence of different concentrations of the drug under investigation. Stereospecific, i.e., opiate receptor related, interaction of ^{3}H-etorphine was determined as the difference in binding obtained in the presence of an appropriate excess of dextrorphan and levorphanol, respectively. The potency of the drugs in inhibiting the stereospecific binding of ^{3}H-etorphine was determined from log-probit plots of the data. It should be noted that since April, 1982, the concentration of ^{3}H-etorphine in the binding assay was reduced from 3.0 nM to 0.5 nM, a concentration approaching the K_D of the radiolabeled opiate. This change was implemented in order to let the determined EC50 approximate the true K_i of a given drug. However, due to the different concentration of the radiolabeled ligand, the EC50s determined since April, 1982 are lower than those obtained previously. For the purpose of reference, Table III contains EC50 values of representative opiates determined in binding assays using 0.5 nM ^{3}H-etorphine.

TABLE III

EC50 of representative opiates in displacing 0.5 nM ^{3}H-etorphine in a membrane preparation from rat cerebrum

Compound	EC50 (nM) -NaCl	EC50 (nM) +NaCl	+Na/-Na
UM 911	14.6	28.3	1.94
Morphine	14.0	23.6	1.69
Dextrorphan	6180	9820	1.59
UM 1071R	1.14	1.55	1.36
Ketazocine	10.7	14.1	1.32
Ethylketazocine	5.22	6.60	1.26
(-)SKF 10047	4.09	3.93	0.96
Etorphine	0.47	0.37	0.79
(-)Cyclazocine	0.85	0.53	0.63
Naltrexone	1.43	0.63	0.44

NOTE: Binding data for these and other compounds, determined in binding assays using 3.0 nM ^{3}H-etorphine, are included in the 1978 and 1981 ANNUAL REPORTS.

INHIBITION OF TWITCH OF ISOLATED SMOOTH MUSCLE PREPARATIONS

In the past, submitted drugs have been evaluated on two smooth muscle preparations, the details of which were described in the 1978 ANNUAL REPORT (Swain et al, 1978). Shown in the following pages are the EC50's for the tested drug alone, for the drug in the presence of naltrexone (a pure opioid antagonist which is more effective against so-called "mu" agonists than against so-called "kappa" agonists), and for the drug in the presence of UM 979 (an antagonist which appears to be more effective against "kappa" than against "mu" drugs) (Smith, 1978). The maximum depression of the electrically induced twitch in each of the preparations is also indicated. The concentrations of both naltrexone and UM 979 used in tests of antagonism are always 10^{-7} M for the guinea pig ileum and always 10^{-8} M for the mouse vas deferens. Recently, the drug evaluation procedure has been modified. The guinea-pig ileal preparation has not proven to be reliable and may give false positive results. Therefore, the preparation is only used as a supplementary assay. Drugs are still evaluated on the mouse vas deferens as described previously.

There have been small additional modifications in procedure. First, naltrexone, 10^{-7} M, is the only antagonist used. Second, the ability of naltrexone, in an equimolar concentration, to reverse the inhibition of the twitch by active drugs, is assessed. Finally, the ability of each drug to reverse the inhibition of the twitch produced by a maximally effective concentration of morphine is measured in order to determine whether the unknown drug has antagonistic activity.

SUMMARY OF TESTS PERFORMED

The compounds which were evaluated at the University of Michigan during the past year and the individual tests which were performed are shown in Table IV. Also shown are dates of Annual Reports in which results are reported of earlier tests on those compounds conducted at Michigan. [Those also performed at the Medical College of Virginia are so indicated (MCV)].

The compounds which were evaluated at the Medical College of Virginia during the past year and the tests performed are shown in Table V. Those also performed at the University of Michigan are so indicated (UM).

TABLE IV

SUMMARY OF TESTS PERFORMED (UM)

NIH	UM	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS	MCV
9450	1305	4276	benzomorphan	1982	1982	1982	-	-	+	+	-	
9830	1295		dihydromorphine	-	-	-	-	-	+	+	-	
9831	1296		dihydromorphine	-	-	-	-	-	+	+	-	
9833	1297		morphine-peptide	-	-	-	-	-	+	+	-	
9835	1299		morphine-peptide	-	-	-	-	-	+	+	-	
9842	1352	-	morphinan	-	-	-	-	-	+	+	-	
9886	1285	4233	phenylmorphan	-	-	-	-	-	+	+	-	
9887	1286	4234	phenylmorphan	-	-	-	-	-	+	+	-	
9888	1287	4243	phenylmorphan	-	-	-	-	+	+	+	-	
9922	1320	4259	phenylpiperdine	-	-	-	-	-	+	+	-	
9929	1311	4260	morphine	1982	1982	-	-	-	+	+	-	
9930	1312	4002	naltrexone	1982	1982	-	-	-	+	+	-	
9938	1321	4269	benzomorphan	-	-	-	-	+	+	+	-	+
9941	1331	4283	naphthylamine	-	-	-	-	-	+	+	-	
9942	1332	4284	naphthylamine	-	-	-	-	-	+	+	-	
9945	1327	4286	phenylmorphan	1982	1982	-	-	-	+	+	-	
9969	1346	4291	isoquinoline	+	-	+	-	-	-	-	-	+
9970	1357	4292	isoquinoline	-	-	-	-	+	+	+	-	+
9974	1361	4295	morphinan	-	-	-	-	-	+	+	-	
9989	-	4299	morphinan	-	-	-	-	-	+	+	-	
9998	1369	-	morphinan	-	-	-	-	+	-	+	-	
10002	1371	4309	naloxone oxime	-	-	-	-	-	+	+	-	
10010	1379	4316	morphinan	-	-	-	-	-	+	+	-	
10016	1383	4318	morphinan	1983	1983	-	-	-	1983	+	-	
10018	1385	-	morphinan	1982	-	1982	-	-	+	+	-	

TABLE IV Continued

SUMMARY OF TESTS PERFORMED

NIH	UM	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	SDS	NW	N	SA	GPI	MVD	BIND	PDS	MCV
10021	1388	4405	phenylmorphan	1982	-	-	-	-	+	+	-	+
10121	-	4338	phenyltoloxamine	+	-	-	-	-	-	-	-	+
10146	-	4339	imidazole	+	-	-	-	-	+	-	-	+
10147	-	4341	naltrexone	+	+	-	-	-	+	+	-	+
10148	-	4342	naloxone	+	+	-	-	-	+	+	-	+
10149	-	4343	naltrexone	+	+	-	-	-	+	+	-	+
10157	-	4339	benzomorphan	+	-	-	-	-	+	-	-	+
10159	-	4350	benzomorphan	+	-	-	-	-	-	-	-	+
10160	-	4351	benzomorphan	+	-	-	-	-	-	-	-	+
10163	-	4352	oxymorphone	+	-	-	-	-	-	-	-	+
10169	-	4361	cyclizine	+	-	-	-	-	-	-	-	+
10170	-	4362	promethazine	+	-	-	-	-	-	-	-	+
10172	-	4367	benzomorphan	+	-	-	-	-	-	-	-	+
10173	-	4368	benzomorphan	+	-	-	-	-	-	-	-	+
10174	-	4363	hydroxyzine	+	-	-	-	-	-	-	-	+
10175	-	4364	diphenhydramine	+	-	-	-	-	-	-	-	+
10186	-	4375	tripelennamine	+	-	-	-	-	-	-	-	+
10187	-	4376	naltrexone	-	+	-	-	-	-	-	-	+
10188	-	4377	naloxone	-	+	-	-	-	-	-	-	+
10189	-	4378	oxymorphone	+	-	-	-	-	-	-	-	+
10249	-	-	normetazocine	+	-	-	-	-	-	-	-	
10292	-	4396	ethylamine	-	-	-	-	-	+	-	-	+
10293	-	4397	ethylamine	-	-	-	-	-	+	-	-	+
10294	-	4398	ethylamine	-	-	-	-	-	+	-	-	+

TABLE V

SUMMARY OF TESTS PERFORMED (MCV)

NIH	UM	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	MOUSE					RAT		MONKEY			UM
				TF	TFvsM	PPQ	HP	N	SM	PPD	SDS	PPT-W	PPD	
8359		4385	Nalbuphine	+	+	+	+	-	-	-	+	-	-	
8509		4232	Phenylmorphan	+	+	+	+	-	-	-	+	-	-	
8683		4403	Meptazinol	+	+	+	+	-	-	-	+	+	-	
8791		4386	Butorphanol	+	+	+	+	-	-	-	+	-	-	
8805		4387	Buprenorphine	+	+	+	+	-	-	-	+[a]	+	-	
8848		4348	Ethylketocyclazocine	+	+	+	+	-	-	+	-	-	-	
9344		4104	Doxpicomine	+	+	+	+	-	-	+	-	-	-	
9736		4196	Morphinan	+	+	+	+	+	-	-	-	-	+	
9938	1321	4269	6,7-Benzomorphan	+	+	+	+	-	-	-	+	-	-	+
9969	1346	4291	Benzooctahydroisoquinoline	+	+	+	+	-	-	-	+	-	-	+
9970	1357	4292	Benzooctahydroisoquinoline	+	+	+	+	-	-	-	+	-	-	+
10021		4405	Phenylmorphan	+	+	+	+	-	-	-	+	-	-	+
10068		4236	14-Hydroxydihydromorphinone	+	+	+	+	-	-	-	+	+	-	
10069		4327	14-Hydroxydihydromorphinone	+	+	+	+	-	-	-	+	+	-	
10070		4328	14-Hydroxydihydromorphinone	+	+	+	+	-	-	-	+	-	-	
10071		4329	14-Hydroxydihydromorphinone	+	+	+	+	-	-	-	+	-	-	
10111		4337	14-Hydroxydihydromorphinone	+	+	+	+	-	-	-	-	-	-	
10121	1388	4338	Phenyltoloxamine	+	+	+	+	+	-	+	+(3 studies)			+

TABLE V Continued

SUMMARY OF TESTS PERFORMED (MCV)

NIH	UM	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	MOUSE TF	MOUSE TFvsM	MOUSE PPQ	MOUSE HP	MOUSE N	RAT SM	RAT PPD	MONKEY SDS	MONKEY PPt-W	MONKEY PPD	UM
10142		4365	6,7-Benzomorphan	+	+	+	+	-	-	-	-	-	-	
10144		4366	6,7-Benzomorphan	+	+	+	+	-	-	-	-	-	-	
10146		4339	Imidazoimidazole	+	+	+	+	+	-	-	+	-	-	+
10147		4341	14-Hydroxydihydro-morphine	+	+	+	+	-	-	-	-	-	-	+
10148		4342	14-Hydroxydihydro-morphine	+	+	+	+	-	-	-	-	-	-	+
10149		4343	14-Hydroxyepoxy-morphinan	+	+	+	+	-	-	-	-	-	-	+
10156		4345	6,7-Benzomorphan	+	+	+	+	-	-	-	+	-	-	
10157		4349	6,7-Benzomorphan	+	+	+	+	-	-	-	-	-	-	+
10158		4346	6,7-Benzomorphan	+	+	+	+	-	-	-	+	+	-	
10159		4350	6,7-Benzomorphan	+	+	+	+	-	-	-	-	-	-	+
10160		4351	6,7-Benzomorphan	+	+	+	+	-	-	-	-	-	-	+
10163		4352	14-Hydroxydihydro-] morphine	+	+	+	+	-	-	-	-	-	-	+
10164		4347	14-Hydroxydihydro-morphine	+	+	+	+	-	-	-	+	-	-	
10169		4361	Cyclizine	+	+	+	+	+	-	-	+	(2 studies)		+
10170		4362	Promethazine	+	+	+	+	+	-	-	+	-	-	+
10171		4369	Epoxyphenylmorphan	+	+	-	+	-	-	-	-	-	-	
10172		4367	Epoxyphenylmorphan	+	+	+	+	-	-	-	-	-	-	+
10173		4368	6,7-Benzomorphan	+	+	+	+	-	-	-	-	-	-	+
10174		4363	Hydroxyzine	+	+	+	+	-	-	-	+	-	-	+
10175		4364	Diphenhydramine	+	+	+	+	-	-	-	+	-	-	+

TABLE V Continued

SUMMARY OF TESTS PERFORMED (MCV)

NIH	UM	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	MOUSE TF	TFvsM	PPQ	HP	N	RAT SM	PPD	SDS	MONKEY PPt-W	PPD	UM
10186		4375	Tripelennamine	+	+	+	+	-	-	-	+	+	-	+
10187		4376	14-Hydroxydihydro-morphinone	+	+	+	+	+	-	-	-	-	-	+
10188		4377	14-Hydroxydihydro-morphinone	+	+	+	+	-	-	-	-	-	-	+
10189		4378	14-Hydroxydihydro-morphinone	+	+	+	+	-	-	-	-	-	-	+
10215		4380	Chlorpheniramine	+	+	+	+	-	-	-	+	-	-	
10216		4381	Cimetidine	+	+	+	+	-	-	-	+	-	-	
10224		4393	Epoxyphenylmorphan	+	+	+	+	-	-	-	-	-	-	
10248		4379	Pyrilamine	+	+	+	+	+	-	-	+	-	-	
10250		4384	Flunixin	+	+	+	+	-	-	-	+	-	-	
10292		4396	Phenylcyclohexene	+	+	+	+	-	-	-	+	-	-	+
10293		4397	Phenylcyclohexene	+	+	+	+	-	-	-	+	-	-	+
10294		4398	Phenylcyclohexene	+	+	+	+	-	-	-	+	-	-	+
10303		4353	Dynorphin (1-13)	-	-	-	-	-	-	-	+	-	-	
10304		4354	Dynorphin (1-10)-amide	-	-	-	-	-	-	-	+	-	-	
10306		4356	Dynorphin (1-6)	-	-	-	-	-	-	-	+	-	-	
10307		4357	alpha-Neo-Endorphin	-	-	-	-	-	-	-	+	-	-	
10308		4358	Vasopressin	-	-	-	-	-	-	-	+	+	-	
10309		4370	Dynorphin (1-8)	-	-	-	-	-	-	-	+	-	-	
10311		4394	14-Hydroxydihydro-morphine	+	+	+	+	+	-	-	+	+	-	
10316		4395	(+)-Thebaine	+	+	+	+	+	-	-	+	-	-	

TABLE V Continued

SUMMARY OF TESTS PERFORMED (MCV)

NIH	UM	MCV	CHEMICAL CLASS AND/OR GENERIC NAME	MOUSE TF	TFvsM	PPQ	HP	N	RAT SM	PPD	MONKEY SDS	PPt-W	PPD	UM
10323		4372	beta-Funaltrexamine	-	-	-	-	-	+	-	-	+	-	
10332		4415	14-Hydroxydihydro-morphine	+	+	+	-	-	-	-	-	-	-	

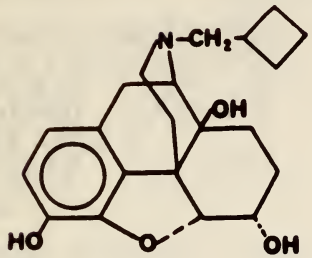
[b] Also, special 9- and 19-hr SDS studies were carried out.

The following Report on Individual Compounds presents the 1984 combined evaluation data from the testing facilities of the Medical College of Virginia (MCV) and the University of Michigan (UM). NIH numbers only are used.

Certain data come only from one laboratory. Thus, the hotplate and Nilsen data come from Dr. Jacobson's laboratory at the NIH, while the rat infusion and other antinociceptive data come from MCV. The quinea pig ileum, rat vas deferens, and binding data come from UM. The monkey data is labeled separately as to its origin.

We hope this new format will make these annual reports easier to reference and more useful.

NIH 8359, 10274 Nalbuphine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)

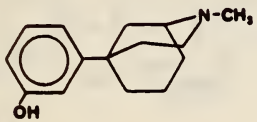
Hot Plate:	approx. 13.0
TF:	10-22% at 1.0, 10.0 & 30.0
TF vs M:	20 % @ 1.0, 63% @ 10.0,69% @ 30.0 & 46% @ 60.0
PPQ:	0% at 1.0, 23% @ 10.0 & 63% @ 30.0

DEPENDENCE EVALUATION IN RHESUS MONKEYS (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
2	10.0		
2	5.0		
1	2.5		
2		3.0	
2			1 ml/kg

NIH 8359 (10274) substituted briefly (90 min) for morphine at the highest dose. Some suppression of withdrawal signs was seen at the lower doses. The compound could not be completely evaluated because drug supply was exhausted. It is recommended that additional studies be conducted.

NIH 8509, 9889 (+)-5-(m-Hydroxyphenyl)-2-methylmorphan



MOUSE ANALGESIA, ED50 (mg/kg)

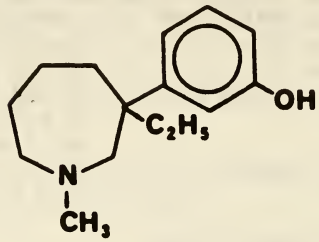
Hot Plate:	0.35 (0.28-0.45)
TF:	4.8 (1.5-15.5)
TF vs M:	0% @ 1.0; 18% @ 30.0
PPQ:	0.5 (0.3-0.9)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
4	8.0		
3	4.0		
3	2.0		
4		3.0	
4			1 ml/kg

NIH 8509 (9889) substituted completely for morphine in 3/4 animals at the highest dose and in all 3 at the next lower dose. The drug acted promptly and had a duration of action of about 90 min. Morphine's duration of action was at least 2½ hours.

NIH 8683 m-(3-Ethyl-1-methylhexahydro-1H-azepin-3-yl)phenol hydrochloride (Metazinol hydrochloride)



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	5.3 (4.0-7.1)
TF:	12.8 (5.8-28.3)
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	1.6 (0.5-5.1)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	3.2		
3	0.8		
2	0.2		
3		3.0	
3			1 ml/kg

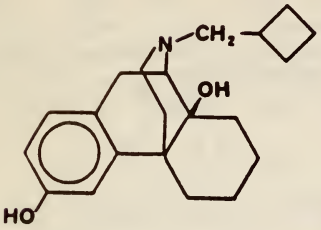
This drug did not substitute for morphine at any of the doses tested. Tremors were noted in some of the animals receiving the 2 higher doses.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (PPt-W)

No. Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	H_2O
2	6.4		
4	3.2		
3	0.8		
2	0.2		
4		0.05	
4			1 ml/kg

NIH 8683 precipitated dose-related withdrawal. Onset of action was prompt and duration was approximately 1 hr. The drug is about 1/150-1/200 as potent as naloxone.

NIH 8791, 10275 Butorphanol Tartrate



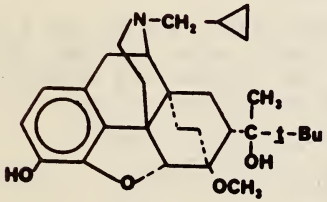
MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: approx. 0.78
TF: Inactive @ 1.0, 10.0 & 30.0
TF vs M: Inactive @ 1.0, 10.0 & 30.0
PPQ: Inactive @ 1.0, 10.0 & 30.0

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	0.5		
3	0.05		
3		3.0	
3			1 ml/kg

The drug did not substitute for morphine and may have exacerbated withdrawal.

NIH 8805, 10276 Buprenorphine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.035 (0.028-0.045)
TF: 0.14 (0.09-0.23)[a]
TF vs M: 1.0 (0.3-3.3)
PPQ: 0.016 (0.005-0.042)

[a]Biphasic curve: 58% @ 1.0; 30% @ 10.0
Naloxone AD 50 vs the TF ED 80 of NIH 10276: 0.15 (0.06-0.36)
Naloxone AD 50 vs PPQ ED 80 of NIH 10271: 0.06 (0.025-0.15)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)
(Regular 15-hr withdrawal, SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	0.64		
3	0.32		
4	0.16		
5	0.08		
5	0.02		
3	0.005		
3	0.0016		
9		3.0	
9			1 ml/kg

NIH 8805, 10276 Continued

In the dose range of 0.005-0.64 mg/kg, NIH 8805 (10276) significantly alleviated many withdrawal signs during the first hour. The drug also reduced the number of withdrawal signs at 0.02 and 0.005 mg/kg during the first 2½ hours. In both cases, however, the drug did not completely substitute for morphine.

(Special 9-hr withdrawal, SDS)

No.	Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
	3	0.32		
	3	0.08		
	3	0.02		
	3		3.0	
	3			1 ml/kg

NIH 8805 (10276) did not substitute for morphine in any of the doses tested.

(Special 19-hr withdrawal, SDS)

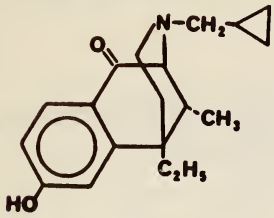
No.	Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	H_2O	(PPt-W)
	3	0.32			
	3	0.08			
	3	0.02			
	3		3.0		
	3			1 ml/kg	

NIH 8805 (10276) partially suppressed withdrawal at the 2 lower doses. In the 19-hour withdrawal test, even morphine did not alleviate the sign vocalizes when the abdomen was palpated and only partially reduced the incidence of many other signs.

(PPt-W) No.	Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	H_2O
	3	0.32		
	3	0.08		
	3	0.02		
	3		0.05	
	3			1 ml/kg

NIH 8805 (10276) precipitated withdrawal in a dose-related manner. Onset of action was prompt and duration of action was more than 2½ hours. Naloxone duration of action is about 1½ hours. At the 2 highest doses, some animals were still vocalizing after abdominal palpation (after morphine at noon and four hours later). The drug appeared to be an irreversible antagonist.

NIH 8848, 10165 2-Cyclopropylmethyl-5-ethyl-8-oxo-9-alpha-methyl-6,-7-benzomorphan methanesulfonate (Ethylketocyclazocine)



MOUSE ANALGESIA, ED50 (mg/kg)

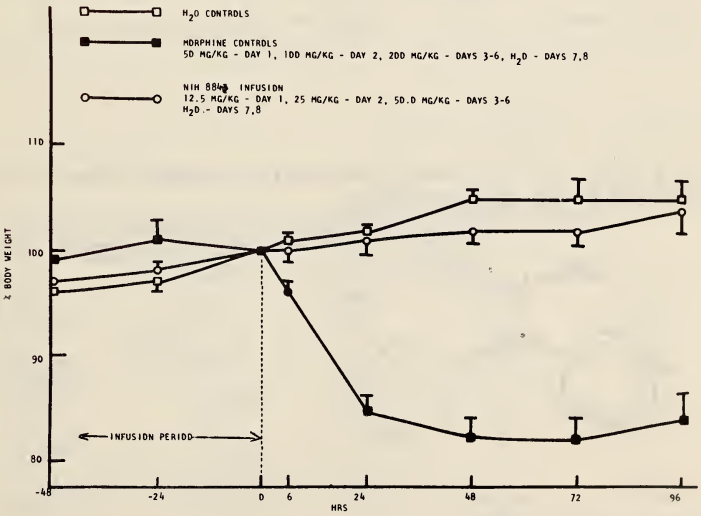
Hot Plate:	0.09 (0.07-0.12)
TF:	0.4 (0.1-1.0)
TF vs M:	Inactive @ 1.0 10.0 & 30.0
PPQ:	0.04 (0.02-0.1)

AD 50 for naloxone vs NIH 10165 in TF: 0.1 (0.04-0.25

AD 50 for naloxone vs NIH 10165 in PPQ: 0.2 (0.04-1.6)

RAT INFUSION (PPD)

As shown in the figure and table ethylketocyclazocine did not produce signs of dependence expressed as either body-weight changes or behavioral-withdrawal signs when infused continuously for 6 days at a dose schedule approximately ½ that of morphine.



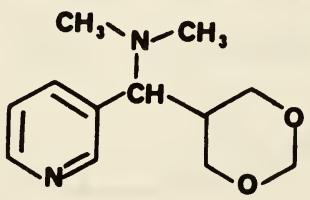
Mean Number of Withdrawal Signs[1] Noted During 1/2 Hour Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and NIH 8848 and Morphine Control

	Hours in Withdrawal				
	6	24	48	72	96
dH_2O Control N = 5	$\bar{x}$ = 0.2	$\bar{x}$ = 1.8	$\bar{x}$ = 3.6	$\bar{x}$ = 2.4	$\bar{x}$ = 1.2
MSO_4 Controls (50 mg/kg - day 1) 100 mg/kg - day 2 200 mg/kg - days 3-6) dH_2O (Days 7, 8) N = 5	$\bar{x}$ = 1.0 p = 0.421	$\bar{x}$ = 15.4 p = 0.004	$\bar{x}$ = 18.8 p = 0.016	$\bar{x}$ = 9.4 p = 0.016	$\bar{x}$ = 3.8 p = 0.210
NIH 8848 Infusion (12.5 mg/kg - day 1 25.0 mg/kg - day 2 50.0 mg/kg - days 3-6) dH_2O (days 7,8) N=5	$\bar{x}$ = 0.6 p = 0.461	$\bar{x}$ = 0.4 p = 0.155	$\bar{x}$ = 3.4 p = 0.461	$\bar{x}$ = 1.4 p = 0.500	$\bar{x}$ = 0.8 p = 0.461

1. Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2. One-tailed test (Mann Whitney U-test).

NIH 9344 (-)-3-[(Dimethylamino)(m-dioxan-5-yl)methyl]pyridine hydrochloride (Doxpicomine)



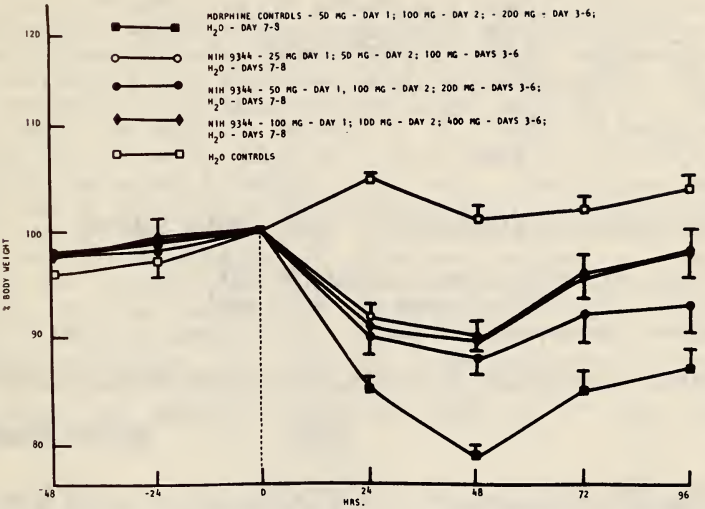
MOUSE ANALGESIA, ED50 (mg/kg)

TF:	Inactive @ 1.0, 3.0 & 10.0
repeat	17.9 (10.2-28.0)
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	6.4 (2.8-14.6)

RAT INFUSION (PPD)

NIH 9344 produced a degree of primary physical dependence at all three dose schedules tested. According to the body weight changes, the degree of dependence which developed was the same at all 3 doses but not as great as that noted for morphine (see figure). Regarding withdrawal signs, there was a dose-related increase at 24 and 72 hours (see table).

NIH 9344 Continued

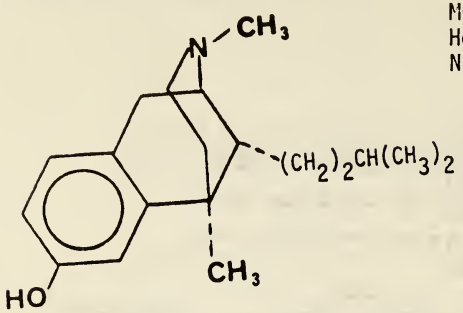


MEAN WITHDRAWAL SCORES[1] AND PROBABILITY VALUES[2] CALCULATED DURING 1/2 HOUR OBSERVATION PERIODS AT SPECIFIED INTERVALS FOR COMPARISONS BETWEEN H_2O ONLY GROUP AND NIH 9344 OR MORPHINE IN A PRIMARY PHYSICAL DEPENDENCE STUDY IN CONTINUOUSLY-INFUSED RATS

	Hours in Withdrawal			
	24 hours	48 hours	72 hours	96 hours
dH_2O Control N = 5	$\bar{x}$ = 0.8	$\bar{x}$ = 1.0	$\bar{x}$ = 1.4	$\bar{x}$ = 2.4
MSO_4 Controls (50, 100, 200 x 4 mg/kg) N = 5	$\bar{x}$ = 10.4 p = 0.004	$\bar{x}$ = 10.0 p = 0.004	$\bar{x}$ = 5.8 p = 0.075	$\bar{x}$ =3.4 p = 0.345
NIH 9344 Inf. (25, 50, 100 x 4 mg/kg) N = 5	$\bar{x}$ = 8.8 p = 0.075	$\bar{x}$ = 6.6 p = 0.004	$\bar{x}$ = 2.6 p = 0.210	$\bar{x}$ = 2.8 p = 0.274
NIH 9344 Inf. (50, 100, 200 N = 5	$\bar{x}$ = 9.4 p = 0.008	$\bar{x}$ = 8.8 p = 0.048	$\bar{x}$ = 5.4 p = 0.028	$\bar{x}$ = 2.2 p = 0.500
NIH 9344 Inf. (100, 200, 400 x 4 mg/kg) N = 4	$\bar{x}$ = 12.0 p = 0.004	$\bar{x}$ = 7.8 p = 0.008	$\bar{x}$ = 5.8 p = 0.095	$\bar{x}$ = 3.8 p = 0.278

1) Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.
2) One-tailed test (Mann Whitney U-Test)

NIH 9450 2,5-Dimethyl-2'-hydroxy-9-alpha-isopentyl-6,7-benzomorphan methanesulfonate



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	14.1 (11.7-17.0)
Nilsen:	19.7 (13.4-29.0)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 361 nM in absence of 150 mM NaCl
EC50 of 622 nM in presence of 150 mM NaCl
Sodium response ratio = 1.72

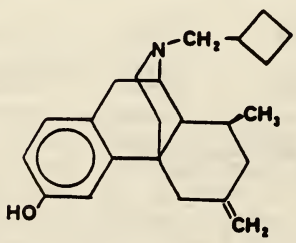
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	19.0 nM	23.2
After naltrexone	1.0 nM	30.2
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		complete reversal

SUMMARY

NIH 9450 is an opioid antagonist without significant agonist action in the mouse vas deferens. It is unusual in the binding assay because it has a sodium reponse ratio that is associated with agonist action.

NIH 9736 N-Cyclobutylmethyl-3-hydroxy-6-methylene-8-beta-methylmorphinan



MOUSE ANALGESIA, ED50 (mg/kg)

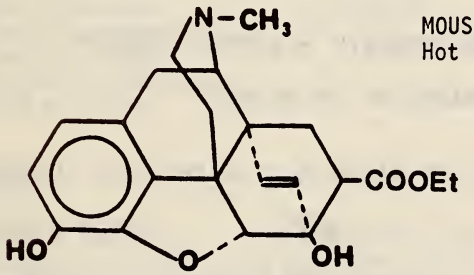
Hot Plate:	60% @ 50.0
Nilsen:	1.3 (0.73-2.4)
TF:	8% @ 0.1; 48% @ 1.0; 12% @ 10.0 @ 8% @ 30
TF vs M:	0% @ 0.01; 48% @ 0.1; 44% @ 1.0; 54% @ 10.0 & 61% @ 30.0
PPQ:	0.02 (0.002-0.18)

NIH 9736 Continued

DEPENDENCE EVALUATION IN RHESUS MONKEYS - PPD (MCV)

Five monkeys were given NIH 9736 every 6 hours. The drug was dissolved in H_2O and given in a volume of 0.25-2 ml/kg. The starting dose was 1.0 mg/kg and it was gradually raised to 13.0 mg/kg by day 12. Salivation and jaw and body sag were noted in some monkeys early in the study and slowing was noted in all the monkeys. Restlessness, wet-dog shakes, vocalizing and scratching were also noted frequently during this period. On day 15, abrupt withdrawal was initiated but no withdrawal syndrome was observed. The study was resumed at 17.0 mg/kg on day 16 but seizures were noted at this dose; the dose was lowered to 12.0 mg/kg on the same day. During this period the signs of slowing, vocalizing, restlessness, wet-dog shakes and scratching were seen. Bleeding was noted at the sites of injection on day 18 and on day 23 ulcers developed at these sites. One male monkey developed severe genital swelling. The study was terminated. No withdrawal syndrome was seen after abrupt and precipitated withdrawal (2.0 mg/kg naloxone). Body weights remained essentially unchanged throughout the study. Despite the fact that NIH 9736 showed little evidence of producing physical dependence, the study had to be terminated early due to the development of skin ulcers. Thus, definitive conclusions regarding the physical-dependence liability of this compound cannot be made.

NIH 9830 Ethyl 6,14-endoetheno-7,8-dihydromorphine-7-beta-carboxylate hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.04 (0.03-0.06)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 18.4 nM in absence of 150 mM NaCl
EC50 of 10.1 nM in presence of 150 mM NaCl
Sodium response ratio = 0.55

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	62.0 nM	89.3
After naltrexone	2.0 uM	86.1
Equimolar concentration with naltrexone		reversal

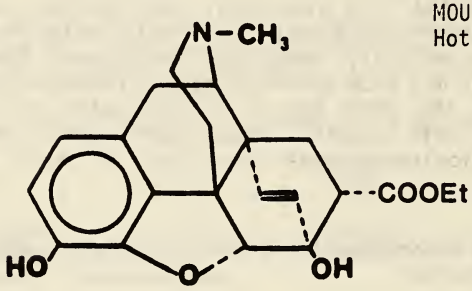
NIH 9830 Continued

	EC50	Maximum Response
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 9830 appears to be a morphine-like agonist upon the mouse vas deferens. It does not differ significantly from morphine either in potency or efficacy. It was as potent in the binding assay as morphine, but NIH 9830 has a smaller sodium response ratio.

NIH 9831 Ethyl 6,14-endoetheno-7,8-dihydromorphine-7-alpha-carboxylate hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.35 (0.27-0.47)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 27 nM in presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

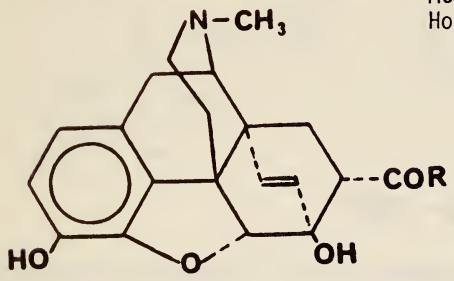
	EC50	Maximum Response
Drug alone	1.04 uM	34.2
After naltrexone	3.13 uM	69.0
Equimolar concentration with naltrexone		marked reversal
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 9831 was a morphine-like agonist upon the isolated mouse vas deferens preparation. It is less potent than morphine, but equally efficacious. It was comparable in potency to morphine in the binding assay.

NIH 9833 N-(6,14-Endoetheno-7,8-dihydromorphine-7-alpha-carbonyl)-L-phenylalanyl-L-leucine ethyl ester hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.83 (0.61-1.1)



R=L-Phe-L-Leu-OEt

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 0.58 nM in presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

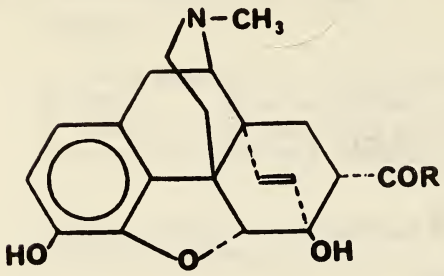
	EC50	Maximum Response
Drug alone	1.16 nM	86.8
After naltrexone	3.52 nM	95.4
Equimolar concentration with naltrexone		slight reversal
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 9833 appeared to be a morphine-like agonist which is equi-effective and about 100 times more potent than morphine. NIH 9833 was also much more potent than morphine in the binding assay.

NIH 9835 N-(6,14-Endoetheno-7,8-dihydromorphine-7-alpha-carbonyl)-L-glycyl-L-phenylalanyl-L-leucine ethyl ester hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 1.1 (0.75-1.5)



R= L-Gly-L-Phe-L-Leu-OEt

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 0.0187 nM in presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	21.8 nM	64.1
After naltrexone	13.7 nM	48.9
Equimolar concentration with naltrexone		reversal
Equimolar concentration with morphine		reversal

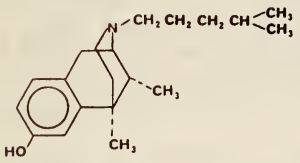
The ability of NIH 9835, 10^{-7} M, to antagonize responses to morphine was evaluated.

	EC50	Maximum Response
Morphine	370 nM	85.3
Morphine plus 9835	4.61 uM	66.8

SUMMARY

NIH 9835 has agonistic action which does not seem to be morphine-like. This drug does have significant opiate antagonistic activity similar to that seen with naltrexone in the vas deferens preparation. NIH 9835 displaces etorphine with an extraordinary potency; it may be a "pure" narcotic of high potency.

NIH 9938 (±)-5,9-alpha-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,-7-benzomorphan hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)

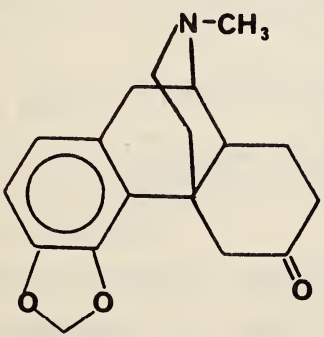
Hot Plate:	8.3 (6.0-11.4)
TF:	3.3 (1.5-7.3)
TF vs M:	0% @ 1.0 & 30.0
PPQ:	2.6 (1.0-7.9)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	12.0		
2	9.0		
2	6.0		
3	3.0		
3		3.0	
3			1 ml/kg

In the dose range tested, NIH 9938 did not substitute for morphine. The monkey receiving the highest dose developed convulsions within 30 minutes. A pentobarbital injection terminated these convulsions.

NIH 9842 (-)-N-Methyl-3,4-methylenedioxy-6-oxomorphinan



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	6.3 (4.3-9.2)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 570 nM in absence of 150 mM NaCl
EC50 of 658 nM in presence of 150 mM NaCl
Sodium response ratio = 1.15

NIH 9842 Continued

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

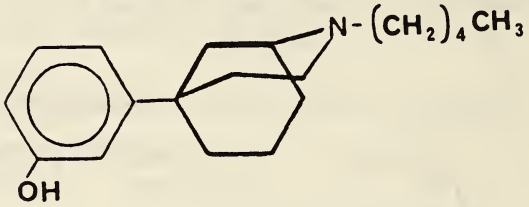
	EC50	Maximum Response
Drug alone	11.6 uM	66.4
After naltrexone	21.3 uM	66.7
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 9842 appears to be devoid of either opiate agonistic or antagonistic activity upon the mouse vas deferens preparation. It, however, displaced etorpine at high concentrations. This is an unusual discrepancy.

NIH 9886 [(-)-(m)-Hydroxyphenyl]-2-n-pentylmorphan hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: inactive
Nilsen: inactive



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 523 nM in absence of 150 mM NaCl
EC50 of 155 nM in presence of 150 mM NaCl
Sodium response ratio = 0.3

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	0.41 nM	29.4
After naltrexone	0.64 nM	32.6
Equimolar concentration after naltrexone		no reversal
Equimolar concentration with morphine		complete reversal

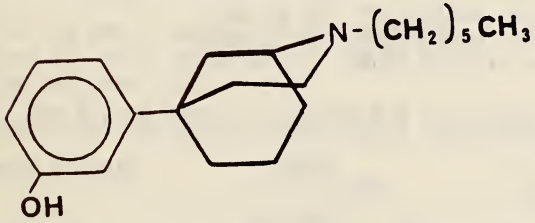
NIH 9886 Continued

SUMMARY

NIH 9886 appears to be an opiate antagonist upon the mouse vas deferens preparation. NIH 9886 low sodium response ratio is associated with narcotic antagonist action. This compound may be a "pure" antagonist with less potency than naltrexone.

NIH 9887 (-)-N-Hexyl-5-(m-hydroxyphenyl)-morphan hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: inactive
Nilsen: inactive



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 117 nM in absence of 150 mM NaCl
EC50 of 150 nM in presence of 150 mM NaCl
Sodium response ratio = 1.28

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

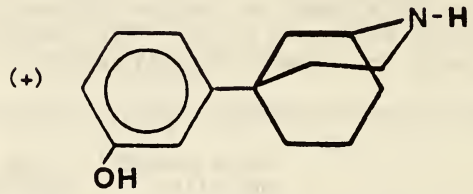
	EC50	Maximum Response
Drug alone	0.47 nM	36.1
After naltrexone	0.54 nM	28.8
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		complete reversal

SUMMARY

NIH 9887 appears to be an opiate antagonist upon the mouse vas deferens preparation without significant agonist actions. NIH 9887 was less potent than naltrexone in the binding assay with a smaller sodium response ratio. This compound may be a "pure" antagonist.

NIH 9888 (+)-5-(m-Hydroxyphenyl)morphan hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: no dose response
Nilsen:



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 232 nM in absence of 150 mM NaCl
EC50 of 263 nM in presence of 150 mM NaCl
Sodium response ratio = 1.13

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA PIG ILEUM

	EC50	Maximum Response
Drug alone	689 nM	97.4
After naltrexone	51 uM	95.2
After UM 979	12 uM	86.7

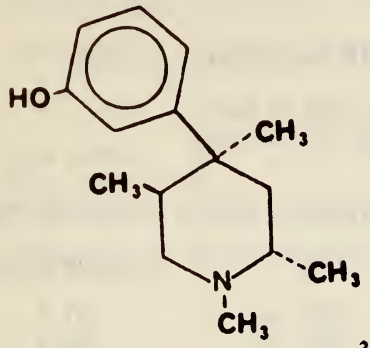
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	2.58 uM	88.4
After naltrexone	11.9 uM	76.4
After UM 979	7.23 uM	64.1

SUMMARY

NIH 9888 appears to be a morphine-like agonist upon both smooth muscle preparations. It was considerally less potent than morphine in all assays.

NIH 9922 3-(1,2-alpha,4-alpha,5-beta-Tetramethyl-4-beta-piperidinyl)-m-phenol,Z-2-butenedioic acid salt



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 2.4 (1.7-3.3)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 84 nM in absence of 150 mM NaCl
EC50 of 141 nM in presence of 150 mM NaCl
Sodium response ratio = 1.67

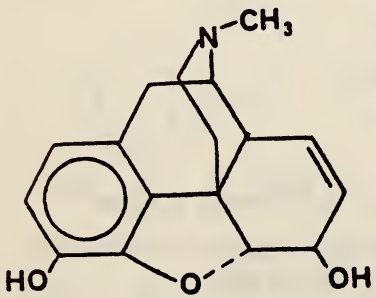
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	8.55 nM	65.2
After naltrexone	33.6 nM	39.3
Equimolar concentration with naltrexone		marked reversal
Equimolar concentration with morphine		slight reversal

SUMMARY

NIH 9922 has both opioid agonistic and antagonistic actions upon the mouse vas deferens preparation.

NIH 9929, 0001 Morphine



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 1.0 (0.7-1.3)
Nilsen: 1.5 (1.1-2.0)

NIH 9929, 0001 Continued

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 50.6 nM in absence of 150 mM NaCl
EC50 of 51.3 nM in presence of 150 mM NaCl
Sodium response ratio = 1.01

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA PIG ILEUM

	EC50	Maximum Response
Drug alone	418 nM	61.8
After naltrexone	23.7 uM	62.5
After UM 979		no inhibition

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

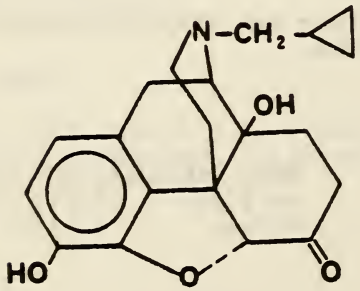
	EC50	Maximum Response
Drug alone	418 nM	100
After naltrexone	3.1 uM	98.2
After UM 979	3.4 uM	98.2

SUMMARY

NIH 9929 has opiate agonist action in each preparation; it is slightly less potent in each assay than morphine.

NIH 9930, 8503 Naltrexone hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: no dose response



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 2.63 nM in absence of 150 mM NaCl
EC50 of 0.97 nM in presence of 150 mM NaCl
Sodium response ratio = 0.37

NIH 9930 8503 Continued

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA PIG ILEUM

	EC50	Maximum Response
Drug alone	1.92 nM	30.2
After naltrexone	3.34 uM	56.7
After UM 979	227 uM	54.4

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

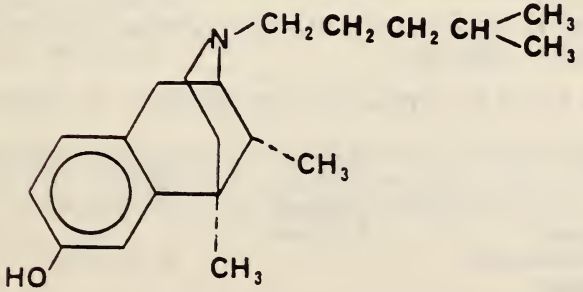
	EC50	Maximum Response
Drug alone	4.9 nM	14.4
After naltrexone	11.3 nM	21.1
After UM 979		completely blocked at 10^{-8} M

SUMMARY

NIH 9930 appears to have opiate agonist activity upon both smooth muscle preparations in addition to other pharmacological effects. The binding data suggest that it will have antagonist activity at slightly higher doses in vivo than naltrexone. Thus, the compound will probably be a strong mixed narcotic agonist-antagonist.

NIH 9938 5,9-alpha-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 8.3 (6.0-11.4)



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 108 nM in absence of 150 mM NaCl
EC50 of 188 nM in presence of 150 mM NaCl
Sodium response ratio = 1.74

NIH 9938 Continued

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA PIG ILEUM

	EC50	Maximum Response
Drug alone	1.28 uM	93.9
After naltrexone	4.77 uM	82.7
After UM 979	3.75 uM	83.3

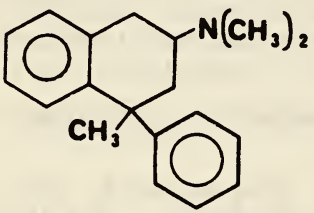
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	687 nM	95.3
After naltrexone	3.13 uM	96.0
After UM 979	2.58 uM	96.0

SUMMARY

NIH 9938 appears to be a narcotic agonist that is less potent than morphine on the basis of comparison to morphine in these assays.

NIH 9941 (-)-trans-N,N-Dimethyl-1,2,3,4-tetrahydro-4-methyl-4-phenyl-2-naphthylamine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 13.1 (9.9-17.3)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

NIH 9941 failed to significantly displace tritiated etorphine up to a concentration of 6000 nM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	3.81 nM	39.4
After naltrexone	4.39 nM	40.7
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		slight reversal

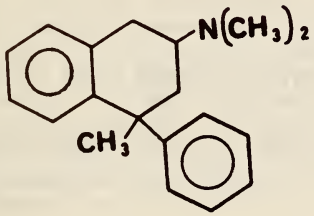
NIH 9941 Continued

SUMMARY

NIH 9941 is devoid of morphine-like agonistic activity. Although in high concentrations it might have very slight antagonistic activity in the vas deferens, it failed to displace etorphine even in high concentrations. Therefore, it is unlikely to have significant narcotic activity in these preparations.

NIH 9942 (+)-trans-N,N-Dimethyl-1,2,3,4-tetrahydro-4-methyl-4-phenyl-2-naphthylamine hydrochloride

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10% @ 20, 40% @ 50, 30% @ 100



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

NIH 9942 failed to significantly displace tritiated etorphine up to a concentration of 6000 nM.

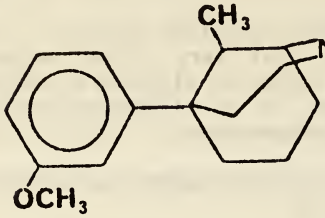
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	3.77 nM	31.5
After naltrexone	3.80 nM	38.9
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		50% reversal

SUMMARY

NIH 9942 is devoid of morphine-like, agonistic activity, but does have some antagonistic activity upon the mouse vas deferens preparations. It fails to displace etorphine even in high concentrations.

NIH 9945 2,9-alpha-5-Dimethyl-5-(m-methoxyphenyl)morphan hydrobromide



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10% @ 20, 50% @ 50 (90% dead @ 100)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

NIH 9945 failed to displace significantly tritiated etorphine up to a concentration of 6000 nM.

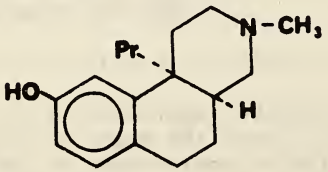
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone		no inhibition
After naltrexone		no inhibition
Equimolar concentration with naltrexone		no inhibition
Equimolar concentration with morphine		no inhibition

SUMMARY

NIH 9945 appears to be devoid of opiate activity in these preparations.

NIH 9969 cis-1,2,3,4,4a,5,6,10b-Octahydro-3-methyl-10b-propylbenz-[f]isoquinoline-9-ol hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 9.0 (6.8-12.0)
TF: 8.8 (3.1-24.8)
TF vs M: Inactive @ 1.0 & 30.0
PPQ: 1.5 (0.5-4.7)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

A dose of 5.6 mg/kg NIH 9969 produced complete suppression of withdrawal. Lower doses (1.0 and 3.0 mg/kg) had little effect on

NIH 9969 Continued

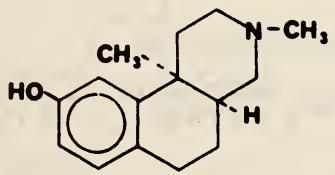
withdrawal. In the non-dependent monkey, 10 mg/kg NIH 9969 produced pupil dilation, decreased movement and scratching that were reversed to some extent by 1.7 mg/kg naloxone.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
2	12.0		
3	8.0		
2	4.0		
3		3.0	
3			1 ml/kg

At the highest doses, NIH 9969 substituted completely for morphine. The onset of action was prompt and duration of action was approximately 7 hours. Morphine also acted promptly and the duration was 2-3 hours. At the intermediate dose, NIH 9969 substituted completely and briefly in 1 of 3 monkeys for approximately 1 hour. Partial substitution was observed in 1 of 2 monkeys receiving the lowest dose. Approximately ¼ as potent as morphine.

NIH 9970 cis-1,2,3,4,4a,5,6,10b-Octhydro-3,10b-dimethylbenz[f]-isoquinolin-9-ol butanedioate (1:1) salt



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	2.6 (1.9-3.7)
TF:	2.7 (1.0-7.4)
TF vs M:	Inactive @ 1.0 & 30.0
PPQ:	1.4 (0.5-3.6)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 1455 nM in absence of 150 mM NaCl
EC50 of 1354 nM in presence of 150 mM NaCl
Sodium response ratio = 0.93

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA PIG ILEUM

At no concentration did NIH 9970 cause an inhibition of the twitch.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	209 nM	60.0
After naltrexone	27.5 nM	32.0
After UM 979	110 nM	47.4

NIH 9970 Continued

SUMMARY

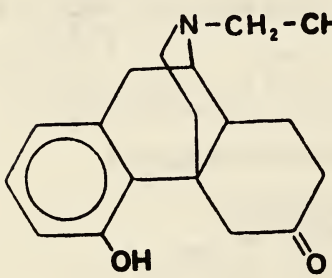
In the binding assay NIH 9970 was not very potent, and it appeared to lack opiate agonist activity upon either smooth muscle preparation.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	24.0		
1	18.0		
3	12.0		
6	6.0		
3	3.0		
3	1.5		
6		3.0	
6			1 ml/kg

Severe ataxia and tremors were seen at the highest dose. The drug did not substitute completely for morphine but it partially suppressed the total number of withdrawal signs especially in the dose range of 3.0-12.0 mg/kg.

NIH 9974 (-)-N-Allyl-4-hydroxymorphinan-6-one



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 1.8 (1.5-2.2)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 114 nM in absence of 150 mM NaCl
EC50 of 223 nM in presence of 150 mM NaCl
Sodium response ratio =1.96

NIH 9974 Continued

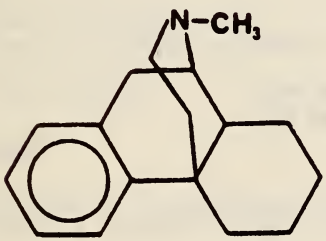
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	671.62 nM	96.2
After naltrexone	6.45 uM	98.4
Equimolar concentration with naltrexone		marked reversal
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 9974 is a morphine-like agonist upon the mouse vas deferens preparation. It is as efficacious but slightly less potent than morphine on this preparation. It is also less potent than morphine in the binding assay, but has a slightly higher sodium response ratio.

NIH 9989 (-)-N-Methylmorphinan d-tartrate



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 2.3 (1.7-3.2)
Nilsen: 2.5 (1.7-3.7)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 375 nM in presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

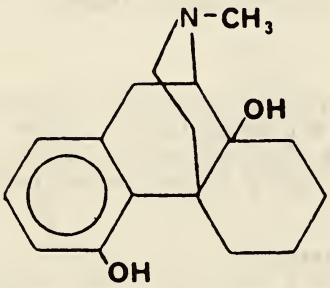
	EC50	Maximum Response
Drug alone	3.02 nM	65.0
After naltrexone	1.53 nM	39.8
Equimolar concentration with naltrexone		partial reversal
Equimolar concentration with morphine		complete reversal

NIH 9989 Continued

SUMMARY

NIH 9989 is an opiate drug with mixed agonist-antagonist activity upon the isolated mouse vas deferens preparation.

NIH 9998 (-)-4,14,Dihydroxy-N-methylmorphinan



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.83 (0.60-1.14)
Nilsen: 1.7 (1.2-2.4)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 108 nM in absence of 150 mM NaCl
EC50 of 115 nM in presence of 150 mM NaCl
Sodium response ratio = 1.06

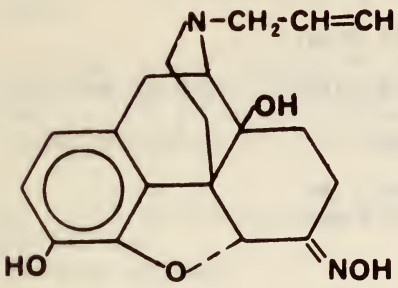
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN GUINEA PIG ILEUM

Only at concentration of 10^{-6} M did NIH 9998 cause a slight (less than 10%) inhibition of the twitch. This response was completely blocked by naltrexone and UM 979.

SUMMARY

NIH 9998 appears to have a very slight opiate-like activity on the guinea-pig ileal preparation and it is somewhat less potent in the binding assay than morphine.

NIH 10002 6-Desoxy-6-isonitrosonaloxone (naloxone oxime)



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: inactive
Nilsen: inactive

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 150 nM in presence of 150 mM NaCl

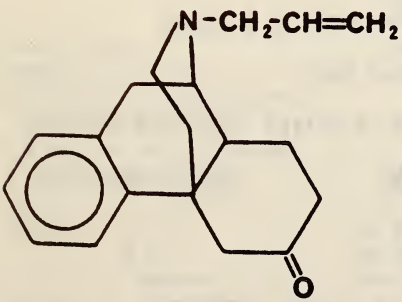
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	1.96 uM	44.9
After naltrexone	0.10 uM	4.4
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		complete reversal

SUMMARY

NIH 10002 is a morphine antagonist upon the isolated mouse vas deferens preparation.

NIH 10010 (-)-N-Allylmorphinan-6-one hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 2.9 (2.1-3.9)
Nilsen: 1.8 (1.3-2.7)

NIH 10010 Continued

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 320 nM in presence of 150 mM NaCl.

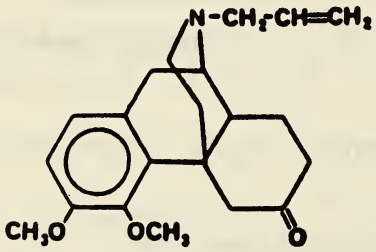
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	186.0 nM	91.9
After naltrexone	15.6 uM	77.0
Equimolar concentration with naltrexone		complete reversal
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 10010 appears to be a morphine-like agonist upon the mouse vas deferens. It does not differ significantly from morphine either in potency or efficacy in this preparation. It was significantly less potent than morphine in the binding assay.

NIH 10016 (-)-N-Allyl-3,4-dimethoxymorphinan-6-one



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 10.6 (8.0-14.0)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 78 nM in presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	123 nM	36.0
After naltrexone	164 nM	24.8
Equimolar concentration with naltrexone		reversal
Equimolar concentration with morphine		reversal

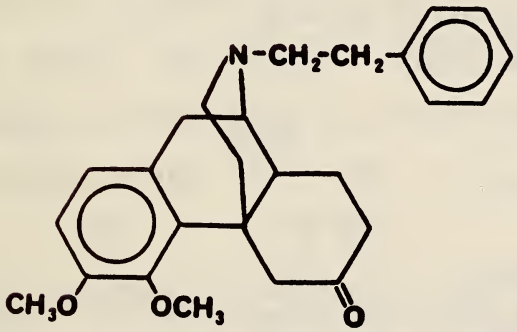
NIH 10016 Continued

SUMMARY

NIH 10016 is much less potent and efficacious than morphine. It appears to have both agonistic and antagonistic properties. It is slightly less potent than morphine and considerably less potent than naltrexone in the binding assay.

NIH 10018 (-)-3,4-Dimethoxy-N-(2-phenethyl)-morphinan-6-one hydrobromide

MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 0.14 (0.10-0.18)
Nilsen: 0.02 (0.017-0.035)



DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 1.75 nM in presence of 150 mM NaCl

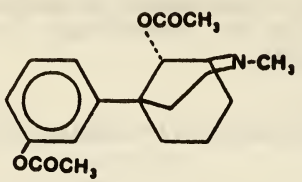
INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	56.1 nM	96.0
After naltrexone	145 nM	96.2
Equimolar concentration with naltrexone		nearly complete reversal
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 10018 appears to be a pure opioid agonist upon the mouse vas deferens. It is more potent and equally efficacious when compared to morphine. In the binding assay, it was more potent than morphine.

NIH 10021 9-alpha-Acetoxy-2-methyl-5-(m-acetoxy)phenylmorphan hydrobromide



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	2.0 (1.4-2.8)
TF:	7.3 (3.6-14.7)
TF vs M:	Inactive @ 30.0, 10.0 & 1.0
PPQ:	2.0 (1.4-2.8)

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 3523 nM in absence of 150 mM NaCl
EC50 of 4246 nM in presence of 150 mM NaCl
Sodium response ratio = 1.20

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	2.88 nM	25.7
After naltrexone	2.04 nM	33.2
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		partial reversal

SUMMARY

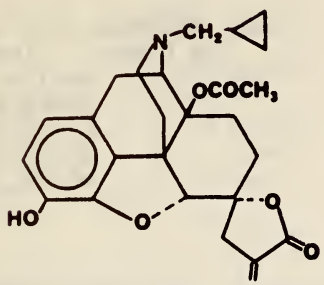
NIH 10021 appears devoid of opioid agonistic activity but might have slight activity as an antagonist in the vas deferens. It is of very low potency in displacing etorphine in the binding assay.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
2	10.0		
2	5.0		
2	1.0		
2		3.0	
2			1 ml/kg

NIH 10021 substituted completely for morphine at the 2 higher doses. Partial substitution was observed at the lowest dose.

NIH 10068 6-beta-(beta-Carboxyallyl)-naltrex-6-alpha-ol-gamma-lactone-14-acetate



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	Inactive
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	0.08 (0.04-0.2)
PPQ:	Inactive @ 0.1, 1.0, 10.0 & 30.0

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	Lactic Acid & H_2O
2	0.05		
2	0.0125		
1	0.003		
2		3.0	
2			1 ml/kg

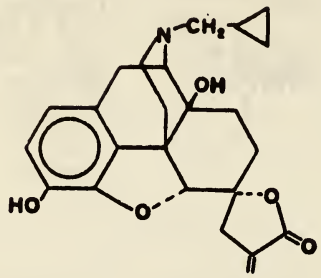
This compound did not substitute for morphine at any of the doses tested. One monkey receiving the highest dose was given morphine because the animal developed severe tremors.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (PPt-W)

No. Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	Lactic Acid & H_2O
2	0.2		
2	0.1		
2	0.05		
2	0.0125		
3		0.05	
3			1 ml/kg

At doses of 0.0125 or more, NIH 10068 precipitated withdrawal; drug acted promptly and the duration of action was at least one hour longer than that of naloxone. The potency is about that of naloxone.

NIH 10069 6-beta-(beta-Carboxyallyl)-naltrex-6-alpha-ol-gamma-lactone



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	Inactive
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	0.1 (0.08-0.2)
PPQ:	20% @ 1.0, 20% @ 10.0 & 29% @ 30.0

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	DMSO & H_2O
2	0.1		
2	0.025		
1	0.006		
2		3.0	
2			1 ml/kg

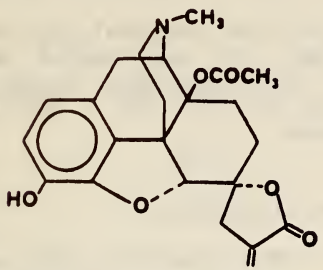
The compound did not substitute for morphine. Instead, it appeared to exacerbate withdrawal at the highest dose.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (PPt-W)

No. Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	DMSO & H_2O
2	1.6		
3	0.4		
2	0.1		
1	0.025		
3		0.05	
3			1 ml/kg

The drug promptly precipitated withdrawal at the 2 higher doses. The duration of action is at least 1 hour longer than that of naloxone but the potency is about 1/10.

NIH 10070 6-beta-(beta-Carboxyallyl)-oxymorphon-6-alpha-ol-gamma-lactone-14-acetate



MOUSE ANALGESIA, ED50 (mg/kg)

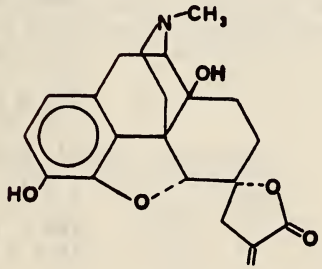
Hot Plate:	4.1 (2.8-6.0)
TF:	8.5 (4.5-15.7)
TF vs M:	4% @ 1.0, 8% @ 10.0 & 20% @ 30.0
PPQ:	2.0 (1.2-3.3)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	Lactic Acid & H_2O
2	12.0		
2	6.0		
2	3.0		
2		3.0	
2			1 ml/kg

In the dose range studied, the drug did not substitute for morphine. Drug supply was exhausted.

NIH 10071 6-beta-(beta-Carboxyallyl)-oxymorphon-6-alpha-ol-gamma-lactone acetic acid salt



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	2.6 (1.8-3.6)
TF:	8.9 (3.7-21.5)
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	0.9 (0.3-3.0)

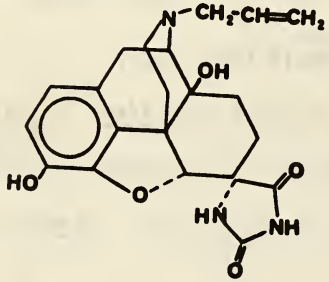
DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	16.0		
3	8.0		
2	4.0		
1	2.0		
3		3.0	
4			1 ml/kg

NIH 10071 Continued

At the highest dose, the drug substituted completely for morphine. It acted promptly and the animal did not require the noon injection of morphine. It substituted for morphine in 2/3 animals at the 8.0 mg/kg dose. Potency is about 1/2 - 1/3 that of morphine. Drug supply was exhausted.

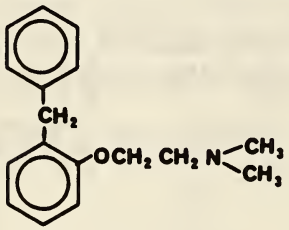
NIH 10111 Naloxone-6-spirohydantoin(6-beta-oxo)



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	10% @ 20.0 & 0.0
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	23% @ 1.0, 17% @ 10.0 & 23% @ 30.0

NIH 10121, 10197 Phenyltoloxamine dihydrogen citrate



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:		40.5 (27.5-59.6)
Nilsen:		40% @ 80
TF:	1	Inactive @ 1.0, 10.0 & 30.0
	2	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	1	Inactive @ 1.0, 10.0 & 30.0
	2	31% @ 0.3, 35% @ 1.0, 31% @ 3.0, 37% @ 10.0 & 34% @ 30.0
PPQ:	1	1.3 (0.3-6.4)
	2	20% @ 1.0, 25% @ 10.0 & 50% @ 30.0

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

NIH 10121 failed to produce marked narcotic agonist or antagonist actions at 5.6, 10 and 30 mg/kg s.c. Further assay was discontinued due to the elicitation of a convulsion upon handling at the highest dose.

NIH 10121 10197 Continued

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV)

STUDY 1 (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
2	30.0		
5	20.0		
5	10.0		
5		3.0	
5			1 ml/kg

At the highest dose, NIH 10121 suppressed withdrawal partially in both monkeys. The drug also partially suppressed withdrawal signs in some monkeys at the 2 lower doses. It acted promptly and the duration of action was at least 2½ hours. Head tremors were noted at the highest dose. Further studies are recommended.

Study 2 (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	30.0		
3	20.0		
1	10.0		
2		3.0	
2			1 ml/kg

We have confirmed the results reported earlier. NIH 10121 substituted partially for morphine at 30.0 and 20.0 mg/kg. One monkey receiving the highest dose had convulsions and was given pentobarbitol, 65.0 mg.

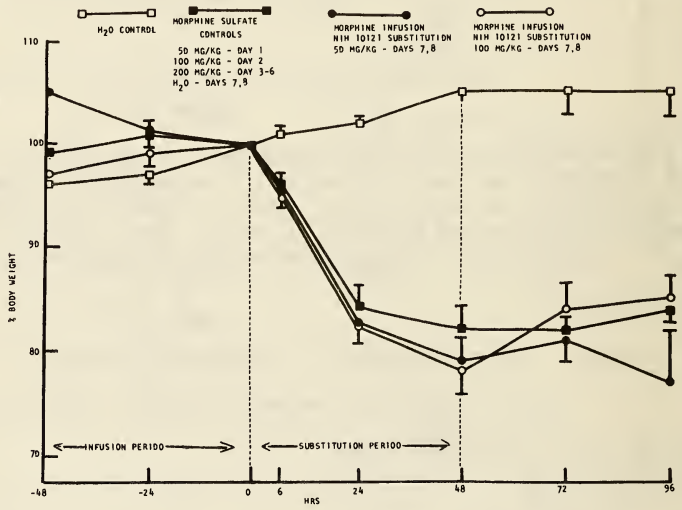
Study 3 (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	16.0		
4	8.0		
3	4.0		
3	1.0		
1	0.25		
7		3.0	
7			1 ml/kg

NIH 10197 partially suppressed withdrawal signs at 0.25-8.0 mg/kg during the first hour. In this dose range the number of signs was suppressed by 50%. Partial suppression does not imply that the drug has morphine-like properties.

RAT INFUSION (SM)

At 50.0 and 100.00 mg/kg/24 hr, NIH 10121 did not substitute completely for morphine in morphine-dependent rats. (See figure and table).



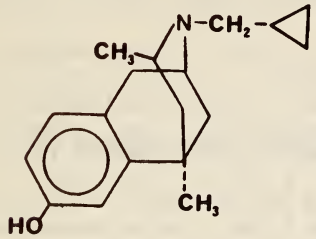
Mean Number of Withdrawal Signs[1] Noted During 1/2 Hour Observation Period at Specified Intervals and Calculated Probability Values[2] for Comparisons Between H_2O Only Group and NIH 10121 and Morphine Control

	Hours in Withdrawal				
	6	24	48	72	96
dH_2O Control N = 5	$\bar{x}$ = 0.2	$\bar{x}$ = 1.8	$\bar{x}$ = 3.6	$\bar{x}$ = 2.4	$\bar{x}$ = 1.2
Morphine Controls (50 mg/kg - day 1) 100 mg/kg - day 2 200 mg/kg - days 3-6) dH_2O (Days 7, 8) N = 5	$\bar{x}$ = 1.0 p = 0.421	$\bar{x}$ = 15.4 p = 0.004	$\bar{x}$ = 18.8 p = 0.016	$\bar{x}$ = 9.4 p = 0.016	$\bar{x}$ = 3.8 p = 0.210
MSO_4 Infusion (50, 100, 200 mg/kg) NIH 10121 Substitution (50 mg/kg - days 7, 8) N = 4 at 6, 24, 48 hrs. N = 3 at 72, 96 hrs.	$\bar{x}$ = 1.0 p = 0.452 vs. Morphine p = 0.500	$\bar{x}$ - 5.3 p = 0.022 vs. Morphine p = 0.016	$\bar{x}$ = 13.8 p = 0.032 vs. Morphine p = 0.322	$\bar{x}$ = 5.8 p = 0.095	$\bar{x}$ = 1.7 p = 0.500
MSO_4 Infusion (above schedule); NIH 10121 Substitution (100 mg/kg - days 7, 8) N = 4 at 6, 24, 48 hrs. N = 3 at 72, 96 hrs.	$\bar{x}$ = 0.8 p = 0.548 vs. Morphine p = 0.452	$\bar{x}$ = 7.3 p = 0.016 vs. Morphine p = 0.175	$\bar{x}$ = 12.0 p = 0.032 vs. Morphine p = 0.278	$\bar{x}$ = 6.0 p = 0.076	$\bar{x}$ = 1.7 p = 0.393

1. Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

2. One-tailed test (Mann-Whitney U-test).

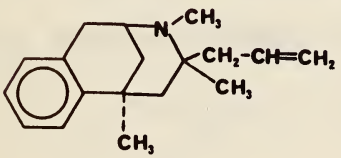
NIH 10142 2-Cyclopropylmethyl-3-beta,5-dimethyl-2'-hydroxy-6,-7-benzomorphan Hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	2.4 (1.9-3.2)
TF:	3.0 (1.0-8.7) 7.9
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	0.2 (0.1-0.6) 3.6
Naloxone vs NIH 10142 in PPQ AD 50:	0.1 (0.05-0.2)

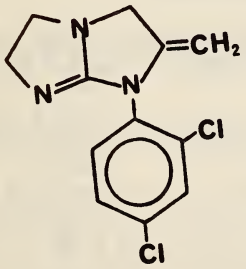
NIH 10144 3-beta-Allyl-2,3-alpha,5-trimethyl-6,7-benzomorphan hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	3.7 (2.7-5.2)
TF:	19% @ 10.0 & 55% 30.0 & 100% @ 60.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	7.0 (3.5-13.7) 1.8

NIH 10146 2,3,5,6-Tetrahydro-6-methylene-7-(2,4-dichlorophenyl)-imidazo[1,2-a]imidazole



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	6.3 (4.7-8.3)
Nilsen:	24.3 (19.7-30.0)
TF:	10% @ 1.0, 25% @ 10%, 19% @ 30.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	2.6 (0.8-8.8)

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	6.03 uM	89.8
After naltrexone	4.46 uM	90.7

NIH 10146 Continued

	EC50	Maximum Response
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		no reversal

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

Neither 3 nor 10 mg/kg NIH 10146 produced typical narcotic agonist or antagonist action. Because the higher dose produced preconvulsive signs in both monkeys, further assay was discontinued.

SUMMARY

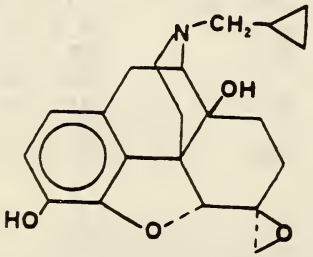
NIH 10146 is devoid of opiate agonistic or antagonistic activity.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	dil HCL & H_2O
3	6.0		
3	3.0		
3		3.0	
3			1 ml/kg

This drug did not substitute for morphine and may have exacerbated withdrawal. Tremors were noted at both doses.

NIH 10147 6-beta-Oxido-6-methylene naltrexone



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	20% @ 50
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	0.007 (0.003-0.197)
PPQ:	Inactive @ 0.1, 1.0, 10.0 & 17% @ 30

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

NIH 10147 was insoluble and EC50's could not be obtained with these preparations.

NIH 10147 Continued

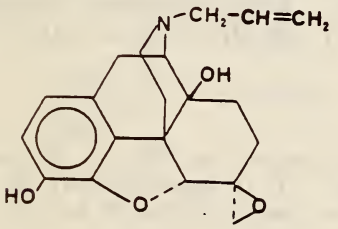
OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

NIH 10147 at 0.1 mg/kg increased the severity of withdrawal signs in the withdrawn monkey. In the non-withdrawn, dependent monkeys, mild withdrawal signs were produced by 0.003 mg/kg, and increased in severity as dose was increased to a maximum of 0.1 mg/kg. It was one third as potent as naloxone in precipitating withdrawal, and had a duration of action of 24 hours.

SUMMARY

This compound is a potent long-acting narcotic antagonist. It is slightly more potent than cyclazocine or WIN 44,441 in precipitating withdrawal. It has a very long duration of action since the monkeys' response to morphine was attentuated even at 24 hrs subsequent to 0.1 mg/kg s.c.

NIH 10148 6-beta-Oxido-6-methylene naloxone



MOUSE ANALGESIA, ED50 (mg/kg)	
Hot Plate:	Inactive
TF:	Inactive @ 1.0, 3.0, 10.0 & 30.0
TF vs M:	0.003 (0.001-0.011)
PPQ:	27% @ 0.3, 12% @ 30.0

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

NIH 10148 was insoluble and EC50's for these preparations could not be obtained.

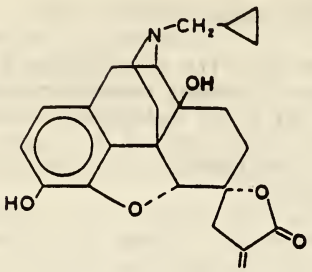
OBSERVATIONS IN THE MORPHINE-DEPENDENT REHESUS MONKEY

NIH 10148 at a dose of 0.1 mg/kg increased the severity of withdrawal in the withdrawn monkey. In the dependent, non-withdrawn monkey, 0.01 mg/kg produced a very mild withdrawal. Increasing doses produced increasing withdrawal signs; 0.06 mg/kg produced severe withdrawal that lasted less than six hours.

SUMMARY

NIH 10148 is a potent (one third the potency of naloxone) narcotic antagonist of relatively short duration of action.

NIH 10149 6-alpha-(beta-Carboxyallyl)-naltrex-6-beta-ol-gamma-lactone



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	30% @ 20
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	0.15 (0.05-0.47)
PPQ:	Inactive @ 1.0, 10.0 & 30.0

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

NIH 10149 was insoluble and EC50's for these preparations could not be obtained.

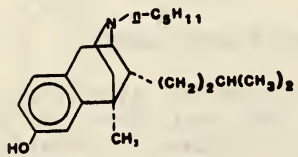
OBSERVATIONS IN MORPHINE-DEPENDENT RHESUS MONKEYS

At a dose of 0.1 mg/kg, NIH 10149 produced an increased withdrawal severity in the withdrawn monkeys. A dose-dependent increase in withdrawal severity was produced by 0.3, 1.0, and 1.8 mg/kg in the non withdrawn monkeys.

SUMMARY

NIH 10149 has narcotic antagonist properties similar to those of naloxone in in vivo preparations. It is approximately 50 times less potent than naloxone and has a long duration of action.

NIH 10156 2'-Hydroxy-5-methyl-9-alpha-(3-methyl)butyl-2-pentyl-6,7-benzomorphan oxalate



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	30% @ 100.0
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	9% @ 1.9, 17% @ 10.0 & 20% @ 30.0

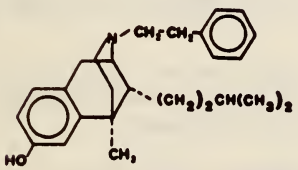
NIH 10156 Continued

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
2	16.0		
2	8.0		
2	4.0		
2		3.0	
2			1 ml/kg

In the dose range tested, NIH 10156 did not substitute for morphine. Restlessness and tremors were seen at the highest dose and the drug appeared to suppress retching. Drug supply was exhausted.

NIH 10157 2'-Hydroxy-5-methyl-9-alpha-(3-methyl)butyl-2-phenethyl-6,7-benzomorphan oxalate



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	50% @ 50
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	46% @ 3.0, 39% @ 10.0[a] & 55% @ 30.0

[a]Propylene glycol controls also active with 43% inhibition.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

NIH 10157 did not inhibit the twitch in concentrations of 10 nm to 10 uM and did not reverse the effects of a maximally effective concentration of morphine.

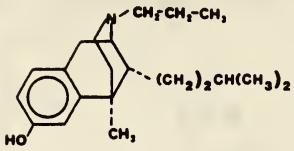
OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

NIH 10157 at 5.6 and 10.0 mg/kg had no apparent effects in withdrawn monkeys. Drug supply depleted.

SUMMARY

NIH 10157 has no apparent narcotic agonist or antagonist effects in these preparations.

NIH 10158 2'-Hydroxy-5-methyl-9-alpha-(3-methyl)butyl-2-propyl-6,7-benzomorphan oxalate



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	No dose response
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	14.8 (9.1-24.0)
PPQ:	7.0 (3.1-16.1)[a]

[a] Naloxone inactive vs NIH 10158 in PPQ test up to 20.0 mg/kg.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
2	5.0		
2	2.5		
2		3.0	
2			1 ml/kg

In the dose range tested, NIH 10158 did not substitute for morphine. Morphine was given to both monkeys receiving the highest dose after 90 minutes because of severe tremors.

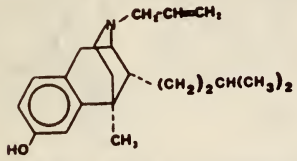
DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (PPt-W)

No. Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	H_2O[a]
2	5.0		
2	1.25		
2		0.05	
2			1 ml/kg

The drug did not precipitate withdrawal at the doses tested. At the highest dose, severe tremors were noted. Drug supply was exhausted.

[a] In some studies the drug was suspended and the volume given was 2 ml/kg.

NIH 10159 2-Allyl-2'-hydroxy-5-methyl-9-alpha-(3-methyl)butyl-6,7-benzomorphan oxalate



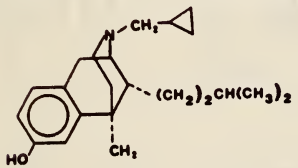
MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	40% @ 50
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	11.2 (4.4-29.0)
PPQ:	10.3 (5.5-19.9)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

NIH 10159 at doses of 1.7-5.6 mg/kg did not alter markedly signs of narcotic withdrawal. At the highest dose, preconvulsive signs were observed. This dose failed to elicit withdrawal in the non withdrawn dependent monkey.

NIH 10160 2-Cyclopropylmethyl-2'-hydroxy-5-methyl-9-alpha-(3-methyl)butyl-6,7-benzomorphan oxalate



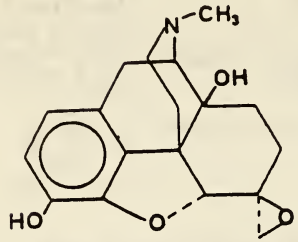
MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	30% @ 50 convulsions)
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	5.5 (3.2-9.5) 2.3
PPQ:	14.4 (10.9-9.1)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

NIH 10160 had little effect in the withdrawn monkey at 3.0 mg/kg, and produced preconvulsive signs at 10.0 mg/kg.

NIH 10163 6-beta-Oxido-6-methylene oxymorphone



MOUSE ANALGESIA, ED50 (mg/kg)

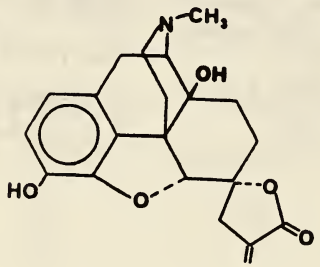
Hot Plate:	0.17 (0.13-0.22)
TF:	0.3 (0.1-0.7)
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	0.02 (0.005-0.05)

Naloxone vs NIH 10163 in TF AD 50
0.01 0.003-0.004)
Naloxone vs NIH 10163 in PPQ AD 50 0.24 (0.1-0.7)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

This compound suppressed abstinence completely in withdrawn dependent monkeys. It was 6 times more potent than morphine and had a shorter duration of action.

NIH 10164 6-alpha-(beta-Carboxyallyl)-oxymorphon-6-beta-ol-gamma-lactone



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	2.6 (1.9-3.7)
TF:	5.2 (3.3-8.0)
PPQ:	2.4 (1.2-4.9)

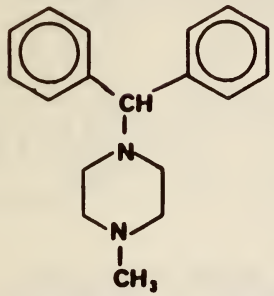
DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	Propylene glycol & H_2O
2	10.0		
2	5.0		
2	2.5		
2		3.0	
2			1 ml/kg

In the dose range studied, NIH 10164 did not substitute for morphine. Muscle spasms were noted in one monkey receiving the highest dose. Drug supply was exhausted.

NIH 10165 - See NIH 8848

NIH 10169 1-Diphenylmethyl-4-methylpiperazine hydrochloride (Cyclizine)



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:		50% @ 50
Nilsen:		23.9 (20.3-28.1)
TF:		Inactive @ 1.0 & 10.0; 21% @ 30.0
TF vs M:		Inactive @ 1.0, 10.0 & 30.0
PPQ:	1	7.4 (3.7-14.9)
	2	29.8 (13.7-67.4)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

This drug suppressed partially the signs of narcotic abstinence at 10 mg/kg. Lower doses were inactive; 30 mg/kg produced strong preconvulsive signs soon after administration and convulsions upon handling at 30 minutes.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV)

Study 1 (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	20.0		
3	10.0		
3	5.0		
3		3.0	
3			1 ml/kg

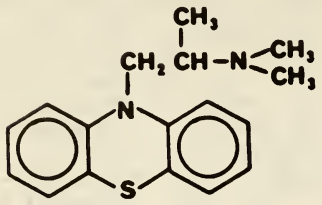
This drug did not substitute for morphine. At the 2 higher doses, severe tremors, stereotyped head movements, and excitation were noted.

Study 2 (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
2	20.0		
2	10.0		
1	5.0		
2		3.0	
1			1 ml/kg

The results of this study confirmed those reported earlier. NIH 10169 did not substitute for morphine. However, at the highest dose after 2 hours, the monkeys did not vocalize when their abdomens were palpated and these muscles were relaxed. Also, at the 2 higher doses tremors were noted.

NIH 10170 N,N-alpha-Trimethyl-1-OH-phenothiazine-10-ethanamine hydrochloride (Promethazine)



MOUSE ANALGESIA, ED50 (mg/kg)		
Hot Plate:		30% @ 30
Nilsen:		12% @ 20
TF:		7-15% @ 1.0, 10.0 & 30.0
TF vs M:	1	4.7 (1.7-13.6)
	2	26% @ 1.0, 30% @ 10.0 & 0% @ 30.0
PPQ:		1.7 (0.6-4.8)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

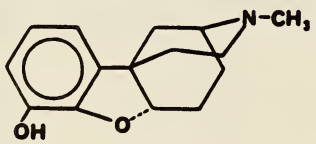
At doses from 5-18 mg/kg, this compound failed to suppress abstinence. It, over this dose range, induced pupil dilation, incoordination, and ataxia. At the highest dose, mild tremor was observed.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
4	20.0		
5	10.0		
3	5.0		
5		3.0	
5			1 ml/kg

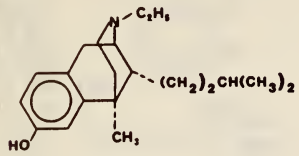
The drug produced dose-related reduction of many withdrawal signs such as rigid abdomen, vocalizes when abdomen palpated, retching and wet-dog shakes. The drug nearly substituted for morphine briefly. Tremors, slowing and ataxia were also observed.

NIH 10171 2,3,4,5,6,6a-Hexahydro-8-hydroxy-1H-4,11b-methanobenzofuro[3,2]azocine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)	
Hot Plate:	10 % @ 50.0
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0

NIH 10172 2-Ethyl-2'-hydroxy-5-methyl-9-alpha-(3-methyl)butyl-6, 7-benzomorphan oxalate

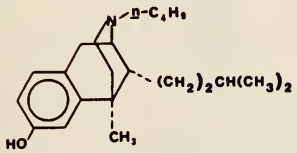


MOUSE ANALGESIA, ED50 (mg/kg)	
Hot Plate:	30% @ 20
TF:	Inatctive @ 1.0, 10.0 & 30.0
TF vs M:	0% @ 1.0, & 10.0; 22% @ 30.0
PPQ:	Inactive @ 1.0, 10.0 & 30.0

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

NIH 10172 at doses of 5.6, 10, and 17 mg/kg had no effect on the withdrawal signs in physically dependent, withdrawn rhesus monkeys. At the two higher doses, mild to marked tremors were observed.

NIH 10173 2-n-Butyl-2'-hydroxy-5-methyl-9-alpha-(3-methyl)butyl-6, 7-benzomorphan oxalate



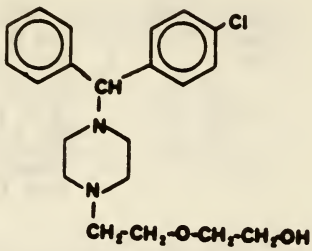
MOUSE ANALGESIA, ED50 (mg/kg)	
Hot Plate:	20% @ 80
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	10% @ 3.0, 55% @ 10.0 & 39% @ 30.0
PPQ:	27.3 (13.3-56.0)

Used 1.5% methylcellulose suspension as vehicle.

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

This compound was studied with a vehicle of 60% emulphor, 20% weak HCl, 20% ethanol. It was heated as well. No effect upon abstinence signs were observed over the dose range of 5-15 mg/kg; tremor was observed at 10 and 15 mg/kg. Drug supply was depleted, preventing a full characterization of effects.

NIH 10174 2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]ethanol hydrochloride (Hydroxyzine)



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	Inactive
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	47% @ 10.0, & 0% @ 20.0
PPQ:	@ 1.0, 3% @ 3.0, 37% @ 10.0 & 43% 30.0

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

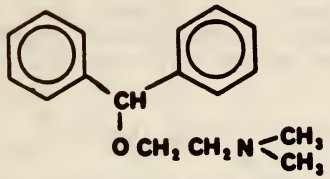
NIH 10174 was given to withdrawn rhesus monkeys in doses of 5.6, 10, 30, 100 mg/kg. Abstinence was not affected at any dose. At the highest dose, prolonged intention tremors, rigidity and slight ataxia were observed.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	30.0		
4	20.0		
4	16.0		
3	8.0		
2	4.0		
7		3.0	
7			1 ml/kg

NIH 10174 substituted partially for morphine at all the doses tested during the first 90 minutes. At the highest dose, 1/3 and at 8.0 mg/kg 4/4 animals did not vocalize when their abdomens were palpated. In addition, the abdominal muscles were relaxed. Some suppression of retching and coughing was also evident. The drug did produce ataxia, slowing and drowsiness at the 3 higher doses. Partial substitution does not necessarily imply that the drug is morphine-like.

NIH 10175 2-Diphenylmethoxy-N,N-dimethylethanamine hydrochloride (Diphenhydramine)



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:		50% @ 30
TF:		Inactive @ 1.0, 10.0 & 30.0
TF vs M:		Inactive @ 1.0, 10.0 & 30.0
PPQ:	1	5.2 (2.5-12.0)
	2	14.8 (4.1-53.1)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

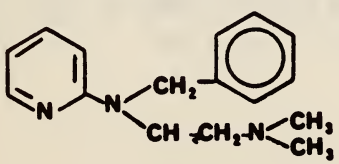
This compound was studied over a 5-30 mg/kg range of doses. Slight suppression of abstinence signs was observed; at no dose was there complete suppression. At 10 and 30 mg/kg, tremor and preconvulsive signs were observed.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	14.0		
4	10.0		
3	7.0		
2	5.0		
2	3.5		
5		3.0	
5			1 ml/kg

NIH 10175 did not substitute for morphine at any of the doses tested. The incidence of tremors was higher at doses of 7.0, 10.0 and 14.0 mg/kg.

NIH 10186 N,N-Dimethyl-N'-2-pyridinyl-1,2-ethanediamine hydrochloride (Tripelennamine)



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	3.9 (1.9-7.9)
TF:	0% @ 1.0, 0% @ 10.0 & 45% @ 30.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	1.3 (0.4-3.7)

NIH 10186 Continued

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

Doses of 1.7, 3.0 and 10.0 mg/kg of NIH 10186 were administered to withdrawn rhesus monkeys. The intermediate dose produced slight suppression of morphine withdrawal. The highest dose produced preconvulsive signs in one monkey (no abstinence suppression), some intention tremor in a second monkey, followed (2-3 hours) by mild suppression of abstinence.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	4.0		
3	1.0		
1	0.25		
3		3.0	
3			1 ml/kg

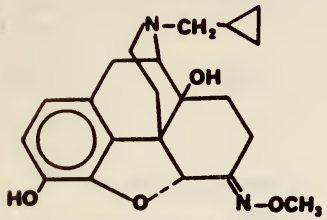
NIH 10186 did not substitute for morphine at 0.25-4.0 mg/kg. At the highest dose, the drug may have exacerbated withdrawal; the incidence of retching and vomiting was increased.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (PPt-W)

No. Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	H_2O
2	8.0		
1	6.0		
3	2.0		
2	0.5		
3		0.05	
3			1 ml/kg

One of the 2 animals receiving the highest dose had convulsions. Pentobarbital (30 mg,i.p.) was given. Salivation, retching, wet-dog shakes, tremors, restlessness and fighting were observed in the other animal. The abdominal muscles were relaxed and this animal did not vocalize when palpated. The animal showed behavior suggesting hallucinations. The drug acted promptly and the duration of action was about 90 minutes. At the lower doses, (tremors at 6.0, and restlessness, fighting, and wet dogs at 2.0) few signs were seen. The drug elicited some but not all of the signs of withdrawal.

NIH 10187 Naltrexone-O-methyloxime

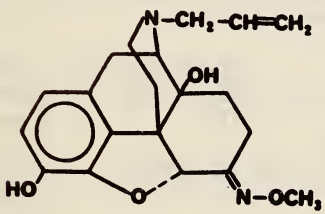


MOUSE ANALGESIA, ED50 (mg/kg)	
Hot Plate:	40% @ 50
Nilsen:	37% @ 50
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	0.08 (0.02-0.3)
PPQ:	3.9 (0.8-20.5)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

Doses of 0.01, 0.03 and 0.056 mg/kg NIH 10187 produced increasingly severe withdrawal signs in the dependent, non-withdrawn monkey. The duration of the withdrawal following 0.03 mg/kg was two hours. This drug is approximately one half as potent as naloxone as a narcotic antagonist in this preparation.

NIH 10188 Naloxone-O-methyloxime

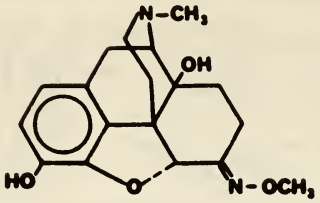


MOUSE ANALGESIA, ED50 (mg/kg)	
Hot Plate:	30% @ 50.0
Nilsen:	Inactive
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	1.9 (0.4-7.8)
PPQ:	Inactive @ 1.0, 10.0 & 30.0

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

Doses of 0.03, 0.1 and 0.3 mg/kg of NIH 10188 produced morphine withdrawal signs of increasing severity in the morphine-dependent, non-withdrawn rhesus monkey. The effects of 0.1 mg/kg lasted approximately 60 min, while those of 0.3 mg/kg lasted at least three hours. This drug is about 10 times less potent than naloxone.

NIH 10189 Oxymorphone-O-methyloxime



MOUSE ANALGESIA, ED50 (mg/kg)

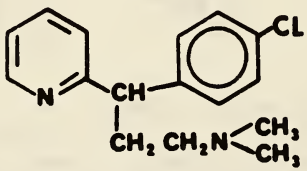
Hot Plate:	0.22 (0.20-0.24)
TF:	0.08 (0.02-0.3)
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	0.24 (0.01-0.05)

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

Doses of NIH 10189, from 0.003 mg/kg, which produced no effect, to 0.1 mg/kg, which produced nearly complete suppression of withdrawal, were evaluated in the 14-hour morphine-deprived, dependent monkeys. The duration of suppression by the highest dose tested was approximately 2 hours. This drug is approximately 100 times more potent than morphine in this test.

NIH 10197 - See NIH 10121

NIH 10215 gamma-(4-Chlorophenyl)-N,N-dimethyl-2-pyridine-propanamine maleate (Chlorpheniramine)



MOUSE ANALGESIA, ED50 (mg/kg)

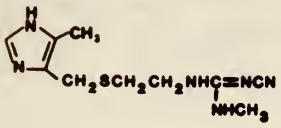
Hot Plate:	10% @ 100.0
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	12% @ 1.0, 16% @ 10.0 & 19% @ 30.0
PPQ:	9% @ 1.0, 22% @ 10.0 & 11% @ 30.0

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	8.0		
3	4.0		
2	1.0		
2	0.25		
3		3.0	
2			1 ml/kg

NIH 10215 did not substitute for morphine in the dose range of 0.25-8.0 mg/kg. Dose related tremors and myoclonic jerks in one animal at 4.0 mg/kg were observed.

NIH 10216 N-Cyano-N'-methyl-N"-[2-[[(5-methyl-1H-imidiazol-4-yl) methyl]thio]ethyl]guanidine(Cimetidine)



MOUSE ANALGESIA, ED50 (mg/kg)

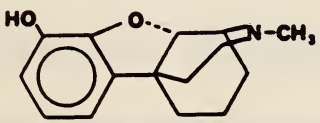
Hot Plate:	10% @ 100.0
TF:	Inactive @ 1.0, 10.0 and 30.0
TF vs M:	Inactive @ 1.0, 10.0 and 30.0
PPQ:	Inactive @ 1.0, 10.0 and 30.0

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	Propylene Glycol & H_2O
1	30.0		
3	15.0		
3	10.0		
3	5.0		
4		3.0	
4			1 mg/kg

In the dose range of 5.0-30.0 mg/kg, NIH 10216 did not substitute for morphine.

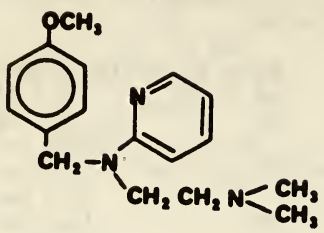
NIH 10224 2,3,4,9b-Tetrahydro-8-hydroxy-2-methyl-1H-1,4a-propano-benzofuro[2,3c]azine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	20% @ 50.0 convulsions @ 60.0
TF:	15% @ 30.0
TF vs M:	6% @ 1.0, 21% @ 10.0, 53% @ 30.0 & 62% @ 60.0
PPQ:	0% @ 10.0, 8% @ 3.0, 34% @ 10.0 & 49% @ 30.0

NIH 10248 Pyrilamine Maleate



MOUSE ANALGESIA, ED50 (mg/kg)

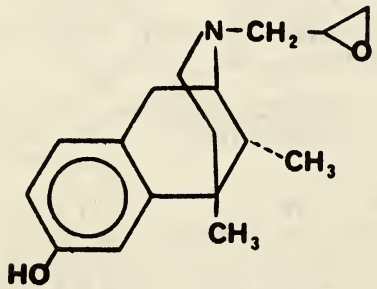
Hot Plate:		32.8 (28.3-38.1)
Nilsen:		17.7 (12.8-38.1)
TF:		Inactive @ 1.0, 10.0 & 30.0
TF vs M:		Inactive @ 1.0, 10.0 & 30.0
PPQ:	1	13.1 (5.7-30.0)
	2	70.6 (39.6-130.1)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	16.0		
4	8.0		
3	2.0		
1	0.25		
4		1.0	
4			1 ml/kg

In the dose range of 0.25-16.0 mg/kg, NIH 10248 did not substitute for morphine. Some tremors were noted at the highest dose. Some suppression of withdrawal signs was observed during the first hour.

NIH 10249 N-(2,3-Epoxypropyl)normetazocine

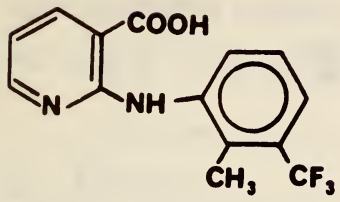


MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: inactive

OBSERVATIONS IN THE MORPHINE-DEPENDENT RHESUS MONKEY (UM)

Administration of 1.0, 3.0 and 5.6 mg/kg NIH 10249 to the withdrawn monkey produced little, if any, change in withdrawal signs. At the highest dose, one monkey showed some abdominal relaxation, but also exhibited stretching and an increase in respiration. This drug does not appear to have marked narcotic agonist or antagonist properties. (Vehicle used: Emulphor, ethanol, and water with heating.)

NIH 10250 Flunixin Meglumine



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	Inactive
TF:	Inactive @ 1.0, 10.0 & 30.0
TF vs M:	0-16% @ 1.0, 10.0 & 30.0
PPQ:	17-56% @ 1.0, 10.0 & 30.0

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	40.0		
4	20.0		
4	10.0		
3	5.0		
1	2.5		
5		3.0	
5			1 ml/kg

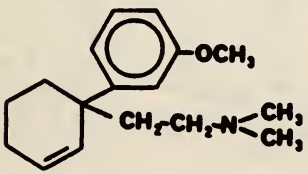
NIH 10250 suppressed the total number of withdrawal signs at the 2 higher doses during the first hour. However, it did not substitute completely for morphine.

NIH 10274 - See NIH 8359

NIH 10275 - See NIH 8791

NIH 10276 - See NIH 8805

NIH 10292 (±)-2-[1-(m-Methoxyphenyl)-2-cyclohexen-1-yl]-N,N-dimethyl ethylamine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	5.2 (3.4-7.9)
TF:	6% @ 1.0, 7% @ 10.0, 39% @ 30.0 & 34% @ 60.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	4.3 (2.2-8.6)

NIH 10292 Continued

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	2.37 uM	54.7
After naltrexone	4.69 uM	51.2
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		no reversal

SUMMARY

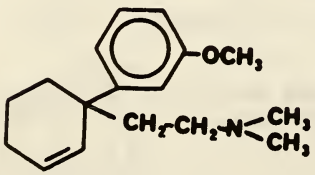
NIH 10292 failed to have significant narcotic activity in these preparations.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	10.0		
3	2.5		
2	0.625		
3		3.0	
3			1 ml/kg

In a preliminary study, a monkey receiving a cumulative dose of 40 mg/kg in 1 hour developed convulsions and died in spite of the fact that pentobarbital (35 mg i.p.) was given. The drug did not substitute for morphine at any of the doses tested.

NIH 10293 (-)-2-[1-(m-Methoxyphenyl-2-cyclohexen-1-yl)]-N,N-dimethyl ethylamine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	4.3 (2.8-6.6) jumping, ataxia & clonic convulsions
TF:	63% @ 60.0, 36% @ 30.0, 0% @ 10.0 & 3% @ 1.0
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	3.0 (1.3-6.8)

NIH 10293 Continued

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC50 of 1100 nM in presence of 150 mM NaCl

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	106 nM	25.3
After naltrexone	91 nM	24.5
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		no reversal

SUMMARY

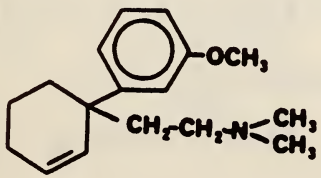
NIH 10293 does not appear to have either opiate agonistic or antagonistic activity upon the isolated mouse vas deferens preparation nor does it displace etorphine at low concentrations.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
1	10.0		
1	5.0		
2	2.5		
1	0.625		
2		3.0	
2			1 ml/kg

At the highest doses, the animal showed severe myoclonic jerks which were treated with pentobarbital (15.0 mg i.p.). The drug did not substitute for morphine.

NIH 10294 (+)-2-[1-(m-Methoxyphenyl)-2-cyclohexen-1-yl]-N,N-dimethyl ethylamine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
Hot Plate: 6.0 (4.5-7.9)
TF: 1 % @ 1.0 & 31% @ 30.0
TF vs M: Inactive @ 1.0, 10.0 & 30.0
PPQ: 1.8 (0.6-5.6)

NIH 10294 Continued

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

NIH 10294 failed to displace tritiated etorphine in concentrations up to 6000 nM.

INHIBITION OF TWITCH OF ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

	EC50	Maximum Response
Drug alone	74.9 nM	22.1
After naltrexone	137 nM	17.4
Equimolar concentration with naltrexone		no reversal
Equimolar concentration with morphine		no reversal

SUMMARY

NIH 10294 appears to be devoid of significant morphine-like agonistic or antagonistic activity upon the isolated mouse vas deferens preparation. NIH 10294 did not have significant activity in the binding assay.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	H_2O
3	5.0		
2	2.5		
3	0.625		
3		3.0	
3			1 ml/kg

NIH 10294 did not substitute for morphine in the dose range of 0.625-5.0 mg/kg. At the 2 higher doses, the drug appeared to exacerbate withdrawal.

NIH 10303 Dynorphin-(1-13): H-Thr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-OH

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/iv)	Morphine (mg/kg/sc)	H_2O
2	0.5		
5	0.25		
5	0.125		
3	0.062		
6		1.0	
6			2 ml/kg

NIH 10303 Continued

Dynorphin-(1-13) at 0.5, 0.25 and 0.125 mg/kg i.v. suppressed withdrawal signs in a dose-related manner within 30 minutes. The effects were waning by 90 minutes.

NIH 10304 Dynorphin-(1-10) Amide

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/iv)	Morphine (mg/kg/sc)	Saline
4	0.5		
4	0.25		
3		3.0	
3			2 ml/kg

Dynorphin-(1-10) amide suppressed withdrawal signs at 0.5 mg/kg i.v.

NIH 10306 Dynorphin-(1-6)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/iv)	Morphine (mg/kg/sc)	Saline
4	0.5		
4	0.25		
3		3.0	
3			2 ml/kg

Dynorphin-(1-6) did not suppress withdrawal signs in morphine-dependent monkeys at either 0.5 or 0.25 mg/kg i.v.

NIH 10307 alpha-Neo-Endorphin

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/iv)	Morphine (mg/kg/sc)	Saline
4	0.5		
4	0.25		
3		3.0	
3			2 ml/kg

alpha-Neo-Endorphin did not suppress withdrawal signs at either 0.25 or 0.5 mg/kg i.v.

NIH 10308 Vasopressin tannate (Pitressin)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (units/sc)	Morphine (mg/kg/sc)	H_2O
4	20		
4	10		
3		3.0	
3			1 ml/kg

Pitressin did not substitute for morphine. This substance may have produced more retching than that seen in the control animals at approximately 3 units/kg.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (PPt-W)

No. Animals	Dose (units/sc)	Naloxone (mg/kg/sc)	H_2O
2	80		
3	40		
4	20		
2		0.05	
2			1 ml/kg

In doses up to approximately 25 units/kg pitression did not precipitate withdrawal in these dependent monkeys.

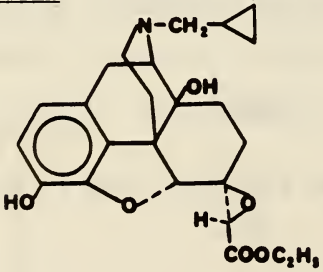
NIH 10309 Dynorphin-(1-8)

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/iv)	Morphine (mg/kg/sc)	Saline
3	0.5		
2	0.25		
3		3.0	
2			2 ml/kg

Dynorphin-(1-8) did not substitute for morphine at 0.5 and 0.25 mg/kg i.v.

NIH 10311 Z-6-Carbethoxymethylene-6beta-oxide naltrexone



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	Inactive @ 20.0 & 50.0
Nilsen:	Inactive
TF:	16% @ 30.0, 17% @ 10.0, 6% @ 1.0
TF vs M:	0.3 (0.1-1.0)
PPQ:	Inactive @ 1.0, 10.0 & 30.0

NIH 10311 Continued

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	Tween 80 & H_2O
3	0.1		
3	0.01		
3	0.001		
4		3.0	
4			1 ml/kg

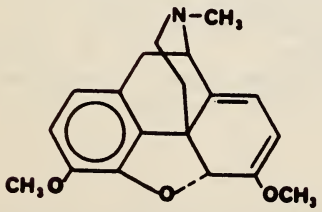
The monkey receiving 1.0 mg/kg in the preliminary study was given morphine (2 x 3.0 mg/kg) to terminate withdrawal. The animal was still vocalizing when palpated 21 hours later in spite of receiving regularly scheduled doses of morphine every 6 hours. The drug did not substitute for morphine at any of the doses tested.

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (PPt-W)

No. Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	Tween 80 & H_2O
3	0.1		
2	0.02		
1	0.01		
1	0.001		
3		0.05	
3			1 ml/kg

Dose-related precipitated withdrawal was observed. The onset of action was rapid and the duration of action much longer than that of naloxone (60-90 min). The animal receiving the highest dose was still vocalizing 1/2 hour after the noon injection of morphine.

NIH 10316 (+)-Thebaine



MOUSE ANALGESIA, ED50 (mg/kg)

Hot Plate:	8.4 (5.8-12.1)
Nilsen:	10.9 (7.7-15.5)
TF:	11.2 (4.8-26.3)
TF vs M:	Inactive @ 1.0, 10.0 & 30.0
PPQ:	1.9 (0.4-7.8)

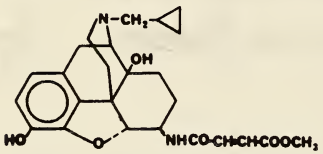
NIH 10316 Continued

DEPENDENCE EVALUATION IN RHESUS MONKEYS (MCV) (SDS)

No. Animals	Dose (mg/kg/sc)	Morphine (mg/kg/sc)	Tween 80 & H_2O
3	12.0		
2	3.0		
2	0.75		
3		3.0	
2			1 ml/kg

NIH 10316 did not substitute for morphine at 0.75-12.0 mg/kg. Drug supply exhausted.

NIH 10323 beta-Funaltrexamine(beta-FNA)



DEPENDENCE EVALUATION IN RHESUS MONKEYS (PPt-W)

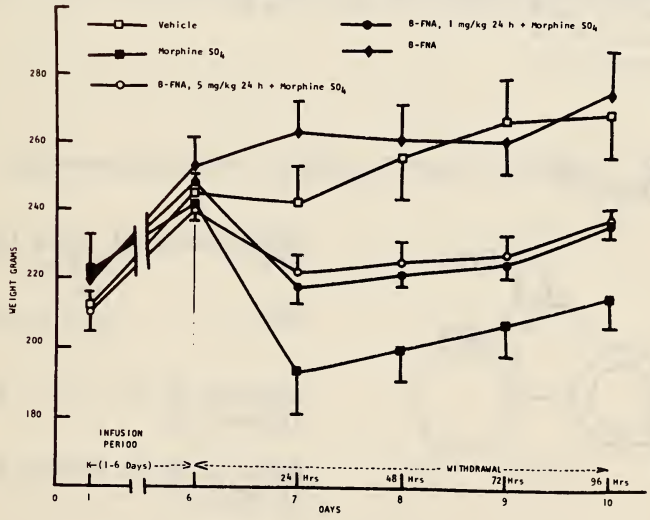
No. Animals	Dose (mg/kg/sc)	Naloxone (mg/kg/sc)	H_2O
5	3.0		
3	10.0		
3		0.05	
3			1 ml/kg

beta-Funaltrexamine precipitated withdrawal in a dose-related manner. The drug produced a full withdrawal syndrome with a rapid onset of action and long duration (> 30 hr). Because we did not want the animals to remain in withdrawal an excessive period of time, they were given morphine after 2 1/2 hrs to terminate withdrawal. The monkeys continued to show signs of withdrawal at the high dose up to 30 hr in spite of the fact that morphine was given regularly every 6 hr.

SPECIAL RAT INFUSION STUDY

As shown in the table, the rats receiving the highest dose of beta-FNA (5.0 mg/kg/24 hr) in combination with morphine failed to show behavioral signs of withdrawal at 24, 48, 72, or 96 hr after abrupt withdrawal was inititated. The lower dose (1.0 mg/kg/24 hr) was partially effective in blocking the development of this

syndrome, i.e., compared with the vehicle controls. Significant differences were calculated at 24 and 48 hr. However, the withdrawal was not as intense as that observed with the morphine controls. The controls receiving only beta-FNA did not show a withdrawal syndrome at any time. Regarding weight loss, the morphine controls lost nearly 20% of their body weight within 24 hours after abrupt withdrawal was inititated (Fig. 1) and were slowly regaining weight thereafter. Those animals receiving either dose of beta-FNA in combination with morphine lost approximately half that amount. The beta-FNA controls and vehicle controls behaved similarly and continued to gain weight throughout the entire study. Since this drug is a selective mu antagonist, these results indicate that weight loss may not be associated exclusively with the mu receptor.



Mean numberof withdrawal signs[a] noted during 1/2 h observation period at specified intervals and calculated probability values[b] for comparisons between vehicle only group and β-FNA or morphine groups alone or groups receiving combinations of β-FNA and morphine.

		Abrupt Withdrawal	Mean Probability Value	
Infusion Period (Days 1-6)	24 (Day 7)	48 (Day 8)	72 (Day 9)	96 (Day 10)
1) Vehicle Control[c] N = 5	1.0 ---	4.4 ---	2.0 ---	0.4 ---
2) Morhpine Controls[d] N= 4	12.8 0.008	21.0 0.008	10.3 0.016	4.5 0.016
3) β-FNA Controls[e] N = 4	1.8 0.278	2.8 0.278	2.3 0.548	0.8 0.548
4) β-FNA (1 mg/kg 24 h)[f] plus morphine N = 4	14.8 0.032	11.5 0.016	6.8 0.206	1.8 0.119
5) β-FNA (5 mg/kg24 h)[g] plus morphine N = 5	0.8 0.421	3.0 0.155	1.6 0.548	0.8 0.242

[a] Hypersensitivity, squealing, aggression, wet dog shakes, rubbing and chewing.

[b] One-tailed test (Mann Whitney U-test).

[c] 8 ml/24 h

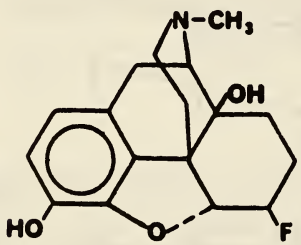
[d] 50.0 mg/kg/24 h, day 1; 100.0 mg/kg/24 h, day 2; and 200.0 mg/kg/24 h, days 3-6

[e] 1.0 mg/kg/24 h, day 1; 2.0 mg/kg/24 h, day 2; 4.0 mg/kg/24 h, days 3-6

[f] 1.0 mg/kg 24 h, days 1-6

[g] 5.0 mg/kg/24 h, days 1-6

NIH 10332 6-Deoxy-6-fluoro-7,8-dihydro-14-hydroxymorphine hydrochloride



MOUSE ANALGESIA, ED50 (mg/kg)
TF: 0.3 (0.2-0.4)
2.5
PPQ: 0.03 (0.02-0.5)
2.4

Naloxone AD 50 in TF: 0.07 (0.04-0.13)

Naloxone AD 50 in PPQ: 0.11 (0.03-0.3)

SELF-ADMINISTRATION STUDIES - MCV

Intravenous self-administration studies were carried out as described previously (Slifer and Balster, 1983). Adult male rhesus monkeys were prepared with chronic intravenous catheters which were protected by a vest and restraining arm arrangement.

SELF-ADMINISTRATION STUDIES Continued

They were trained to lever press under a fixed-ratio 10 schedule for intravenous cocaine hydrochloride during daily one-hour sessions. Injections were 1.0 ml delivered over 10 sec. When responding was stable, test solutions were substituted for four days. Between each substitution the subjects were returned to cocaine for at least three days. The vehicle for each test drug (usually 0.9% saline) was also substituted for four days. The data from the last three days of each substitution was used in the data analyses. A dose was considered to function as a reinforcer in a particular subject if the mean for the three days exceeded the vehicle mean and the ranges did not overlap. Cocaine baseline injection rates were determined for each subject from the average of the three-day means preceding each dose substitution for each drug or drug pair tested.

Five compounds (NIH 7410, 7569, 7571, 8509 and 9802) were evaluated this year. The results are shown in the accompanying tables.

NIH 7410 alpha-metazocine: (±)-2,5,9-alpha-trimethyl-1'hydroxy-6,7-benzomorphan HCl
NIH 7569 Levometazocine: (-)-2,5,9-alpha-trimethyl-2-'hydroxy-6,7-benzomorphan HBr
NIH 7571 alpha-(+)-metazocine: (+)-2,5,9-alpha-trimethyl-2'-hydroxy-6,7-benzomorphan HBr

SELF-ADMINISTRATION

Drug	Dose (mg/kg/inj)	Mean # of Injection[a]	Range of Means[b]	#Self-Administering Tested[c]
Cocaine·HCl	50	45.7	37.8 - 51.2	3/3
Saline	--	9.0	5.9 - 11.7	--
NIH 7410·HCl	3	33.2	11.7 - 62.3	1/3
	10	71.2	11.3 - 145.0	2/3
	30	63.2	38.0 - 112.7	3/3
	100	65.0	57.3 - 74.0	3/3
NIH 7569·HBr	1	20.9	8.0 - 23.3	2/3
	3	26.7	12.7 - 35.0	1/3
	10	43.3	13.3 - 103.3	1/3
	30	73.0	22.0 - 161.3	2/3
NIH 7571·HBr	3	8.8	3.7 - 14.0	0/3
	10	13.3	9.0 - 19.7	1/3
	30	12.8	8.7 - 18.0	0/3
	100	31.9	3.3 - 56.3	2/3

[a]Mean number of injections per 1-hr session over last 3 days of each 4-day substitution for 3 subjects.
[b]Range of 3-day means for the individual subjects tested with each treatment.
[c]Subjects were considered to self-administer a dose when the range of injection rates for that dose did not overlap the range of injection rates for saline.
Conclusion: NIH 7410 and NIH 7569 were self-administered above control levels at least at one dose in each of the subjects tested. NIH 7571 was self-administered at 100 mg/kg/inj in 2 of the 3 subjects. Limited supplies precluded further testing of NIH 7571.

NIH 9882 and 8508 (-)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride
NIH 8509 (+)-5-(m-Hydroxyphenyl)-2-methylmorphan hydrochloride

INTRAVENOUS SELF-ADMINISTRATION

Drug	Dose (mg/kg/inj)	# of Subjects	Mean # of Injections[a]	Range of Means[b]	#Self-Adminstering / #Tested
Cocaine·HCl	30 or 50	5	57.8	32.3 - 97.0	5/5
Saline	--	5	8.9	3.3 - 20.3	--
NIH 9882	1	1	18.7	--	0/1
	3	4	26.0	7.0 - 52.3	3/4
	10	4	37.6	12.3 - 71.0	2/4
	30	4	45.3	8.0 - 87.0	4/4
	100	2	25.4	21.3 - 29.5	2/2
NIH 8509	1	1	17.0	--	0/1
	3	3	39.5	3.3 - 70.3	2/3
	10	4	53.7	1.3 - 117.0	3/4
	30	4	48.9	14.0 - 74.3	3/4
	100	1	47.3	--	1/1

[a]Mean number of injections per 1-hr session over last 3 days of each 4-day substition for all subjects tested with each treatment.
[b]Range of 3-day means for the various subjects tested with each treatment.
[c]Subjects were considered to self-administer a dose when the range of injection rates for that dose did not overlap the range of injection rates for saline.
Conclusion: Both NIH 9882 and NIH 8509 were self-administered above control values at least at one dose in each subject tested.

ACKNOWLEDGEMENTS

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NIH 9998 (UM 1369)
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NIH 10018 (UM 1385)
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NIH 10021 (MCV 4405, UM 1388)
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NIH 10068 (MCV 4326)
See 6β-(β-Carboxyallyl)-naltrex-6α-ol-γ-lactone-14-acetate
NIH 10069 (MCV 4327)
See 6β-(β-Carboxyallyl)-naltrex-6α-ol-γ-lactone
NIH 10070 (MCV 4328)
See 6β-(β-Carboxyallyl)-oxymorphon-6α-ol-γ-lactone-14-acetate

NIH 10071 (MCV 4329)
See 6β-(β-Carboxyallyl)-oxymorphon-6α-ol-γ-lactone acetic acid salt

NIH 10111 (MCV 4337)
See Naloxone-6-spirohydantoin (6β-oxo)

NIH 10121 (NIH 10197, MCV 4338, MCV 4373)
See Phenyltoloxamine dihydrogen citrate

NIH 10142 (MCV 4365)
See 2-Cyclopropylmethyl-3β,5-dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride

NIH 10144 (MCV 4366)
See 3β-Allyl-2,3α,5-trimethyl-6,7-benzomorphan hydrochloride

NIH 10146 (MCV 4339)
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NIH 10147 (MCV 4341)
See 6β-Oxido-6-methylene naltrexone

NIH 10148 (MCV 4342)
See 6β-Oxido-6-methylene naloxone

NIH 10149 (MCV 4343)
See 6α-(β-Carboxyallyl)-naltrex-6β-ol-γ-lactone

NIH 10156 (MCV 4345)
See 2'-Hydroxy-5-methyl-9α-(3-methyl)butyl-2-pentyl-6,7-benzomorphan oxalate

NIH 10157 (MCV 4349)
See 2'-Hydroxy-5-methyl-9α-(3-methyl)butyl-2-phenethyl-6,7-benzomorphan oxalate

NIH 10158 (MCV 4346)
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NIH 10159 (MCV 4350)
See 2-Allyl-2'-hydroxy-5-methyl-9α-(3-methyl)butyl-6,7-benzomorphan oxalate

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NIH 10163 (MCV 4352)
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NIH 10164 (MCV 4347)
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NIH 10170 (MCV 4362)
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NIH 10188 (MCV 4377)
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