National Institute on Drug Abuse

Research 34

MONOGRAPH SERIES

Problems of Drug Dependence 1980

Proceedings of the 42nd 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, 1980

Proceedings of the 42nd Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc.

Editor: Louis S. Harris, Ph.D.

NIDA Research Monograph 34

February 1981

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

National Institute on Drug Abuse
Division of Research
5600 Fishers Lane
Rockville, Maryland 20857

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402

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ACKNOWLEDGMENT

The papers in this monograph were presented or read by title at the 42nd Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc., in Hyannis, Massachusetts, on June 16-19, 1980. Opinions expressed in the papers are those of the authors and do not necessarily reflect the opinions or official policy of the National Institute on Drug Abuse; Alcohol, Drug Abuse, and Mental Health Administration; Public Health Service; or the Department of Health and Human Services.

Library of Congress catalog card number 81-600016

DHHS publication number (ADM) 81-1058
Printed 1981

NIDA Research Monographs are indexed in the *Index Medicus.* They are selectively included in the coverage of *Biosciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts,* and *Psychopharmacology Abstracts.*

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Foreword

In each year's calendar of scientific events related to drug abuse, the Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc., is an occasion of outstanding importance.

The membership of the CPDD represents a broad spectrum of expertise that includes pharmacology, clinical medicine, psychiatry, public health, chemistry, and the social sciences. The Committee maintains liaison with Government regulatory and research agencies, with the pharmaceutical industry, with national and international agencies that are interested in drug dependence and abuse, and with educational and treatment facilities.

The proceedings of each annual CPDD meeting are a comprehensive gathering of reports on current research in all aspects of drug abuse and drug dependence. Topics presented in Problems of Drug Dependence, 1980 include the effects of drugs on the central nervous system, their pharmacological action, biological disposition, safety, abuse potential, and clinical usefulness. Annual progress reports of NIDA-supported dependence studies of new compounds are included, in addition to the 40 papers presented and 6 papers read by title at the 42nd Annual Scientific Meeting in Hyannis, Massachusetts, on June 18-20, 1980. There is also an extensive index. Some of the papers have been condensed by the authors to meet space limitations of this volume.

In the belief that readers with widely diverse interests will find this timely review of value, the National Institute on Drug Abuse is pleased, for the second year, to publish in its Research Monograph series the Proceedings of the Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc.

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

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Dynorphin

Nathan B. Eddy Memorial Award Lecture

A. Goldstein

It is indeed a very great honor to be chosen as recipient of the 1980 Nathan B. Eddy Memorial Award. Dr. Eddy was one of the truly great pioneers in the field of opiabe research and, in more ways than one, my own research owes inspiration to what he contributed to our field. I have stood here so often before, on the platform at previous meetings of CPDD, presenting some research finding, while Dr. Eddy -- right there in the second row -- listened and took notes. I can remember if one said anything at all that lacked sufficient experimental evidence or was too speculative, he would look up suddenly, then scribble more vigorously in his notebook. And afterwards, in corridor discussion , one would have to defend one's conclusions against his sharp and perceptive criticisms.

It has been said that if we accomplish anything at all in science, it is because we can stand on the shoulders of giants. Besides Dr. Eddy, there have been other giants in our field -- some of them in this room today -- upon whose shoulders I was lucky enough to stand. This Committee on Problems of Drug Dependence has played a role of extraordinary importance in nurturing the environment in which fruitful concepts and hypotheses about the opiates could develop. Since I was a product and a beneficiary of that environment, the occasion of this award seems an appropriate time, and this meeting an appropriate place, to acknowledge that debt.

Another major influenza in stimulating my early research in the opiate field was Vincent Dole. His conviction that opiate addiction was fundamentally a biochemical disorder -- a "metabolic disease"-- had a very great influence on me in the late 1960's. My clinical interest in heroin addiction was a direct outcome of what Dr. Dole was saying and doing. But more than that, his view of the disorder encouraged me to seek the molecular mechanisms of opiate action, and consequently to develop, in 1971, the conceptual approach and practical technique for identifying the opiate receptors (Goldstein 1971).

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In late 1974 and early 1975, Terenius and Wahlstrom (1974) and the Aberdeen group (Hughes, 1975) reported that the opiate receptors really did have endogenous ligands which could be extracted from brain. Then, at the May 1975 International Narcotic Research Conference, when the structures of the endogenous ligands from brain were still unknown, my group reported our discovery of opioid activity in pituitary extracts. Our first paper (Teschemacher et al., 1975) described a material from fresh bovine pituitary glands which had all the properties later shown to characterize β-lipotropin- (61-91) , now known as β--endorphin. Indeed, when later in 1975, the sequence of methionine-enkephalin, reported by Hughes and Kosterlitz and their colleagues (Hughes et al., 1975), proved to be identical to the sequence 61-65 of β·-lipotropin, my group, in collaboration with Dr. C.H. Li, immediately demontrated the opioid activity of β·-endorphin (Cox et al., 1976). Simultaneously, Smyth's group (Bradbury et al., 1976) published essentially the same finding.

Our second paper (Cox et al., 1975) dealt with an opioid peptide obtained from a crude porcine ACTH extract. Its properties were clearly different from those of β·-endorphin or any fragment of β-lipotropin. It was much more basic, its apparent molecular weight was only about half as great, its naloxone-reversible inhibitory effect in the guinea myenteric plexus preparation could not be washed out as quickly, and its biologic activity was more easily destroyed by trypsin. Most important of all, its biologic activity was completely resistant to cyanogen bromide -- a reagent that attacks methionine residues -- whereas the activity of every opioid peptide containing mathionine-enkephalin is destroyed by this reagent. The cyanogen branide result suggested the possibility that this nor- β·-endorphin-like "slow-reversing endorphin" might contain leucine-enkephalin, and this turned out to be the case.

We took a long tine to isolate enough of the new endorphin for partial sequencing. Fortunately, Drs. Leroy Hood and Michael Hunkapiller, at Caltech, were perfecting their microsequencing technology at the same time. When we finally obtained two micrograms in a state suitable for sequencing, they had reached the point where this amount was sufficient. The first 13 residues are now know with certainty (Goldstein et al., 1979), but there is some doubt about the next four (we think there are seventeen in all) . Fortunataly, all the potency of the natural peptide -- and an extraordinary potency it is -- was displayed by the synthetic tridecapeptide.

The natural peptide was named dynorphin in recognition of its great potency (Creek prefix dyn = power). Indeed, dynorphin is in a class by itself. For example, in the guinea pig myenteric plexus preparation it is fully 50 times more potent, on a molar basis, than β·-endorphin, 190 times more potent than normorphine and 700 times more potent than leucine-enkephalin.

By removing one residue at a time from the carboxy terminal of dynorphin-(1-13), my colleague Charles Chavkin was able to ascertain which residues were critically important for the potency, using the myenteric plexus preparation as an assay. All 12 possible fragments in which the amino terminal Tyr^{1} remained intact were prepared and purified to homogeneity. The results can be summarized as follows: 1) The -COOH of Lys^{13} is not required, as the methyl ester is fully active, and COOH-terminally extended peptides(like natural dynorphin) retain full potency. 2) Removal of Lys^{13} causes a loss of potency but this has been show to be due to interference by the negatively charged free -COOH on Leu^{12}, and removal of Leu^{12} restores potency to nearly that of dynorphin-(1-13). 3) There are twocritically important basic residues, removal of which causes major loss of potency; these are Lys^{11} and Arg^{7}.

Our present picture of the dynorphin receptor is shown in figure 1. The important point here is that the "alkaloid pocket," occupied by Tyr-Gly-Gly-Phe, or even the "leucine-enkephalin pocket" occupied by Tyr-Gly-Gly-Phe-Leu, represents only a small part of the extensive recognition site in this opiate receptor.

The high potency of dynorphin-(1-13) is not restricted to the guinea pig myenteric plexus preparation, but two properties of the peptide make it difficult to assess potency accurately in membrane

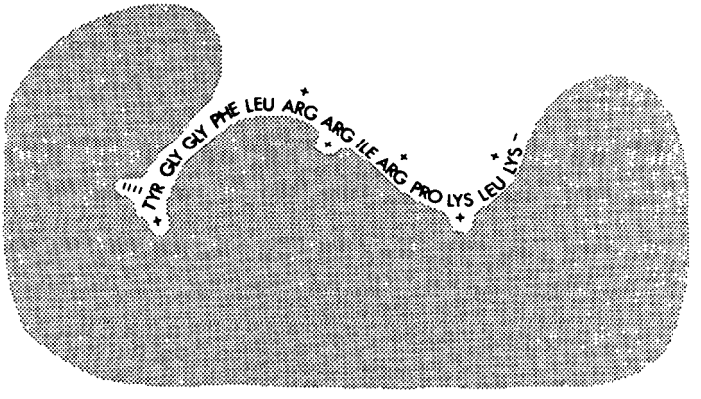

Fig. 1. Hypothetical model of the dynorphin receptor, showing the "alkaloid pocket," which accommodates Tyr-Gly-Gly-Phe, the anionic site accommodating the protonated terminal amino group, and a postulatad H bond involving the phenolic OH group. There are two additional anionic sites, critically placed to accommodate Arg^{7} and Lys^{11}.

radioreceptor binding assays. Most important, this peptide (and natural dynorphin too) is "sticky", i.e., it is adsorbed very rapidly to glass and plastic surfaces, to the matrix of chromatographic media, and to biological membranes. If a "sticky" peptide is not vary potent, there is no problem, because relatively high concentrations will be used, and the adsorptiw losses will be only a small fraction of the total. However, when a "sticky" peptide is vary potent, like dynorphin, the major fraction of what is present may be lost by adsorption. This is illustrated in figure 2. The radioreceptor binding assay was carried out with neuroblastoma X glioma NG-108-15 cell membranes, well washed, with ^{3}H-D-Ala^{2}-D-Leu^{5}-enkephalin as radioligand. At the end of the usual one-hour incubation at 23°, the amount of dynorphin-(1-13) free in the aqueous medium was measured by radioimmunoaassay (see below). The log dose response curve at the right is based on the added (nominal) concentrations, that at the left upon the measured (actual) free concentrations. It is evident that the true IC_{50} (about 200 pM) qualifies the peptide as at least as potent here as in the myenteric plexus preparation.

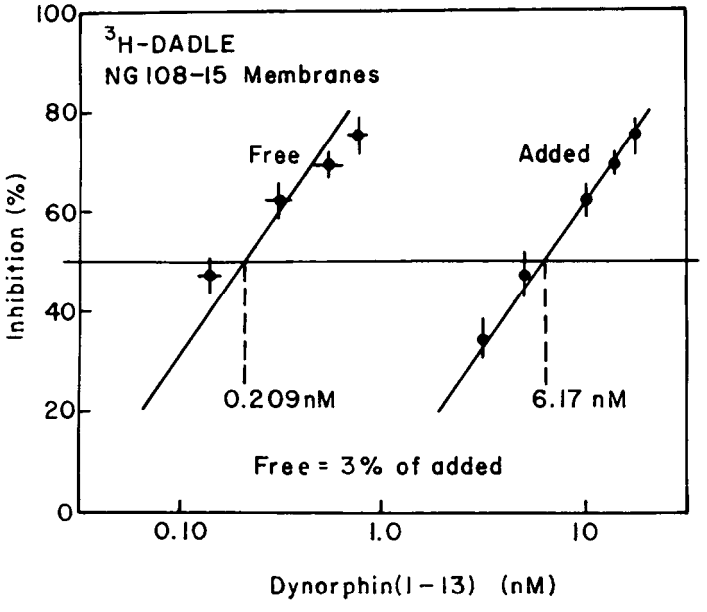

Fig. 2. Radioreceptor binding assay with NG-108-15 cell membranes, showing, at left, the true potency of dynorphin-(1-13), based on radioimmunoassay of free peptide in the supernatant solution, and at right, the apparent potency based on total added peptide. Most of the added dynorphin-(1-13) is adsorbed nonspecifically to membranes or to tube walls.

In order to learn about the distribution of natural dynorphin, it was essential to develop a good radioimmunoassay (RIA). One of the rabbits immunized with dynorphin-(1-13) coupled to thyroglobulin produced a wry sensitive and highly specific antiserum, as illustrated in figure 3. We can detect a few fmol of dynorphin-(1-13), the IC_{50} is 50 pM final concentration in the 0.3-ml incubation mixture, and the specificity is outstandingly good, in that leucine enkephalin is not recognised even at 10 million times the IC_{50} of dynorphin-(1-13). Another opioid peptide that contains leucine endephalin -- α-neo-endorphin -- crossreacts only at about 10^{-4}%. Finally, this antiserum, "Lucia," is indifferent to Tyr^{1} and also to Lys^{13}, and therefore should recognize both COOH-terminally and NH_2-terminally extended dynorphin pepdides.

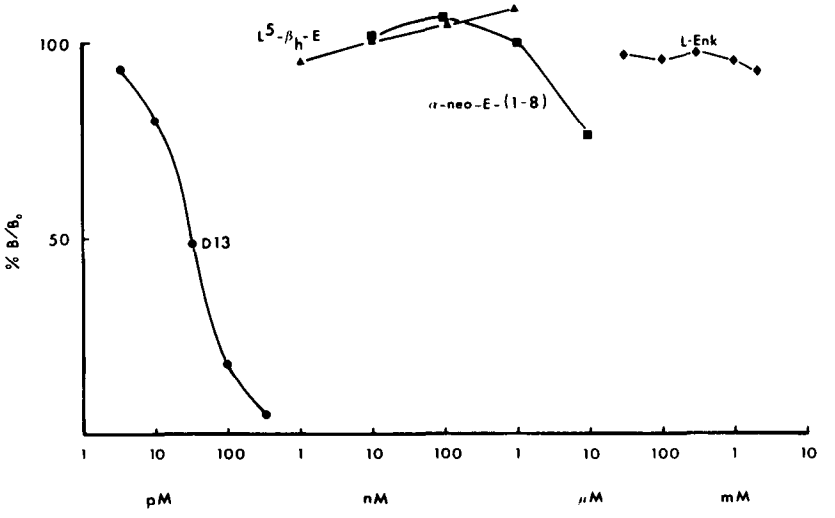

Fig. 3. Radioimmunoassay of dynorphin-(1-13) with "Lucia" antiserum. ^{125}I-labelled dynorphin-(1-13) was displaced by various concentrations of nonradicactive dynorphin-(1-13), at left. These are final concentrations in 0.3-ml incubation mixture. Low crossreactivity with related peptides is shown in curves at right. There was no detectable crossreactivity with β-andorphin (not shown).

Figure 4 shows an assay of an extract of rat pituitary posterior lobe after removal of intermediate lobe tissue. The upper graph shows the parallelism of extract and standard curves, the lower graph shows the loss of immunoreactivity after treatment with

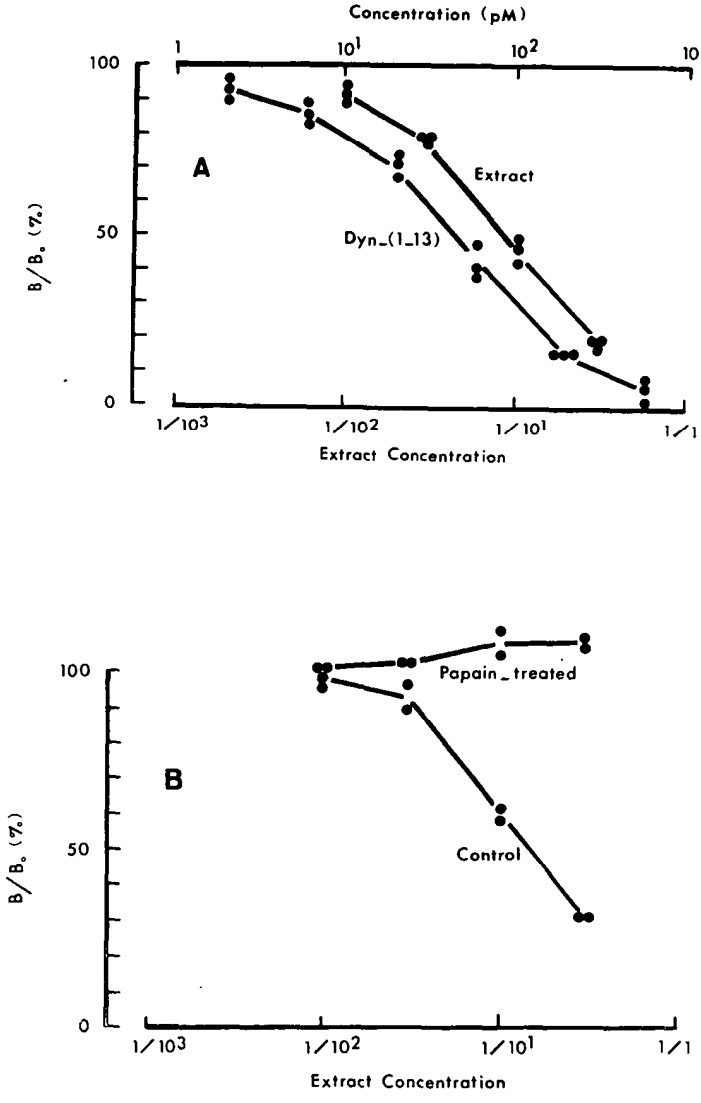

Fig. 4. Dynorphin immunoreactivity in rat pituitary posterior lobe. Top = pituitary extract (right) and dynorphin-(1-13) standard (left). Bottom = pituitary extract treated with papain and with heat-inactivated papain ("control").

papain, thus demonstating the peptides nature of the dynorphin immunoreactivity. In the pituitary, dynorphin is primarily a pars nervosa peptide.

Gel permeation chromatography in 4 M guanidine hydrochloride reveals the presence of two immunoreactive peaks from porcine pituitary posterior lobe. A major peak co-elutes with an α-endorphin marker (MW 1.7 K) , a minor peak co-elutes with a β-endorphin marker (MW 3.4 K) . Similar results are obtained with rat posterior lobe. Rat brain contains two very similar peaks to those in pituitary, and also peaks of larger molecular weight, which could be precursor ("pro-dynorphin") peptides.

Rat brain contains immunoreactive dynorphin in many regions, and the concentration is especially high in spinal cord. The material in spinal cord does not seem to have a supra-spinal origin, since immunoreactivity does not decrease below the level of a transection. My colleague, Dr. Brian M. Cox, has identified inmunoreactive dynorphin in rabbit dorsal root ganglia. Dr. Stanley Watson, using "Lucia" antiserum and immunohistochemical technique, has found immunoreactive dynorphin in large cells of rat supra-optic nucleus, and also in both the myenteric plexus and the submacous plexus of guinea pig ileum. An interesting question is whether any or all "leucine-enkephalin" previously localized by immunohistochemistry may in fact 12 dynorphin , since some leucine-enkephalin antisera do recognize dynorphin-(1-13). In the pars nervosa of rat pituitary, we have made measurements with sufficiently specific antisera to be certain that in this tissue, leucine-enkephalin and immunoreactive dynorphin are both present in about equal amounts. But we do not yet know if leucine-enkephalin can arise from dynorphin, as seems to be suggested by the Arg^6-Arg^7 pair, since double basic resides are often signals for peptide processing.

Dynorphin is in some ways the long-sought counterpart of β-endorphin, namely, a long peptide that attains leucine-enkephalin instead of methionine-enkephalin at its NH_2-terminus. Although studies with naloxone blockade indicate many highly significant functions of endorphins, no function has yet been associated with any particular endorphin . The most important research challenge of the coming years is certainly to find out which endorphin does what. Only then will we uderstand the physiologic role of dynorphin and how it relates to the roles of the other opioid peptides.

In summary, dynorphin is a very potent opioid neuropeptide with wide distribution in the central and peripheral nervous systems and in pituitary. The function of dynorphin have not yet been studied at all. It is appealing to imagine that opiate addiction is associated with disturbed regulation of an endogenous opioid, as I first proposed at a 1973 symposium (Goldstein, 1975). Perhaps this new endorphin will shed light on the problem of opiate dependence.

For the convenience of those who are interested in the historical record, I include below, in addition to the references cited in the text, a chronological annotated bibliography on dynorphin. All the research described here was supported by grants DA-1199, DA-7063, and DA-0054 from the National Institute on Drug Abuse.

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DYNOPHIN: Chronological summary, to June 1980

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-- The properties of this substance, extracted from fresh bovine pituitary glands, were those later found to characterize beta-endorphin (see Cox et al., 1976, above).

B.M. Cox, K. Opheim, H. Teschemacher, A. Goldstein. A peptide-like substance from pituitary that acts like morphine. 2. Purification and properties. Life Sci. 16:1777-1782, 1975.

-- The properties of this substance, obtained from a basic extract of porcine pituitary (crude ACTH), were very different from the substance described above. The differences from β-endorphin and all β-endorphin fragments ware the subject of further publications -- some of which are listed below -- as the material was purified.

S. Gentleman, M. Ross, L.I. Lowney, B.M. Cox, A. Goldstein. Pituitary endorphins. In Opiates and Endogenous Opioid Peptides, H.W. Kosterlitz, Ed., Elsevier/North Holland, Amsterdam, 1976, pp. 27-34.

M. Ross, T.P. Su, B.M. Cox, A. Goldstein. Brain endorphins. In Opiates and Endogenous Opioid Peptides, H.W. Kosterlitz, Ed., Elsevier/North Holland, Amsterdam, 1976, pp. 35-40.

-- These two papers describe further the properties of the non-β-endorphin opioid peptide in pituitary, and demonstrate its presence also in brain. Outstanding characteristics were : (1) its strong basicity, which could only be accounted for by Arg residues; (2) its resistance to cyanogen bromide treatment, indicating it does not contain a critical Met residue, and suggesting, therefore, that it might contain Leu-enkephalin; (3) its sensitivity to tryptic digestion, which was greater than that of β-endorphin; (4) its apparent molecular weight, only about half that of β-endorphin; (5) the slow reversal of its activity in the myenteric plexus preparation upon washing.

B.M. Cox, S. Gentlemen, T.P. Su, A. Goldstein. Further characterization of morphine-like peptides (endorphins) from pituitary. Brain Res. 115:285-296, 1976.

-- Further purification, confirmation of the strong basicity, and indication that the non-β-LPH endorphin is degraded by brain membranes.

L.I. Lowney, S.B. Gentleman, A. Goldstein. A pituitary endorphin with novel properties. Life Sci. 24:2377-2384, 1979.

-- "Slow-reversing endorphin", purified further but still not to homogeneity. Demonstration of predominance of this material in posterior (neurointermediate) lobe of beef pituitary.

A. Goldstein, S. Tachiban, L.I. Lowney, M. Hunkapiller, L. Hood. Dynorphin-(1-13), an extraordinarily potent opioid peptide. Proc. Nat. Acad. Sci. USA 76:6666-6670, 1979.

-- Sequence through 13 residues (YGGFLRRIRPKLK), demonstration that synthetic dynorphin-(1-13) is about as potent as natural dynorphin - in myenteric plexus preparation 190 times normorphine, 50 times β-endorphin. Information about bahavioral effects in rats, and rapid degradation in contact with brain membranes or in vivo.

V.E. Ghazacossian, C. Chavkin, A. Goldstein. A specific radioimmnoassay for the novel opioid peptide dynorphin. Life Sci. 26:75-86, 1980.

-- Sensitive RIA (IC50 17 fmol per assay tube), no cross-reactivity with Leu-enkephalin at 20 million times the concentration. Major losses of dynorphin-(1-13) by adsorption to glass and plastic surfaces.

A. Goldstein, V.E. Ghazarossian. Immunoreactive dynorphin in pituitary and brain. Proc. Nat. Acad. Sci. USA In press, 1980.

-- Application of the RIA to determination of immunoreactive dynorphin in rat, porcine, and bovine pituitary, and in rat brain and spinal cord. Immunoreactive dynorphin is concentrated primarily in parsnervosa of pituitary. It is also widely distributed throughout the central nervous system.

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Increasing Life Span; Changing Disease Patterns; Changing Life Styles: The Role of Government

J. L. Steinfeld

As you meet this year to discuss problems of drug dependence, I thought it might be useful to review briefly the changing health problems in the United States.

As the nation was born, the major health problems were yellow fever, smallpox, scurvy, dysentery, malaria, puerperal fever and childhood diseases occurring in epidemics. The United States, through first the Marine Hospital Service and later the United States Public Health Service, played a major role in improving nutrition, food and water supplies, sanitation, excretion disposal, and discovering and implementing immunization practices.

If we are not to repeat history, we must be familiar with it. The Commissioned Corps of the PHS, threatened with extinction just a decade ago for having outlived its usefulness, is thriving again with the National Health Service Corps, Center for Disease Control, National Institutes of Health, and Alcohol, Drug Abuse, and Mental Health Administration among other units. A similar period in the preceding century was tumultuous just prior to and during the Civil War, when marine health and hospital officers were appointed politically by local Customs officials from the Treasury Department, and the physicians so appointed were accused of performing faulty examinations on Union soldiers and others, thus permitting escape from military duty for payment of legal tender at the time. Following the Civil War, during which the Marine Hospital System was neglected, Congress, after a national study debated many recommendations and then in 1870, federalized the Marine Hospital System and set up a para-military organization for the Marine Hospital Service with physicians appointed to a uniformed service after passing a competitive qualifying

examination, with a Surgeon General as its Chief. President Ulysses S. Grant appointed Dr. John M. Woodworth, hero of General Sherman's march through the South, as the first Surgeon General. I want to emphasize that it was over a century ago that the U.S. saw the ending of a politically appointed national health corps, and the beginning of a quasi-independent professional group of health officials. There was another rupture following World War I, again politically inspired, which led to the creation of the Veterans Administration Hospital and health disability programs.

The Public Health Service's job was clearly cut out for it after the Civil War -- as U.S. citizens moved westward to the Pacific and the country absorbed many thousands of immigrants. Health status in the United States improved slowly, such that a child born around the turn of the century (1900) could expect to live 47 years. Currently the expectation at birth is 73 years. Most of this increase in longevity occurred between 1900 and 1950, resulting from decreased childhood deaths from infections and parasitic diseases. Since 1950 approximately five years have been added to life expectancy at birth and some of this recent increase results not only from antibiotics and improved technology other than drugs, but also results from a decreased death rate from cardiovascular disorders including hypertension and stroke in middle age (particularly true since 1966).

Life expectancy in the United States is not the highest in the industrialized world, but is respectable. The period 1975-1980 provides some fascinating vital statistics. There are 105 male babies born for every 100 female babies. By age 20-24, the ratio is 100 to 100 and that male increase in mortality is determined more by life style characteristics than susceptibility to disease; i.e., males have higher mortality from accidents, including automobile accidents, suicides, homicides, and accidental drug overdoses. By age 65 there are 79 men living for every 100 women and by age 85, there are only 47 men for every 100 women!! A male born in 1976 could expect to live 69 years and female 76 years.

Among young adults, violent deaths account for 75% of deaths among the 15-24 year age group. One half of all deaths from ages 5 to 14 years and 25 to 34 years are the result of violence.

With an increasing life span, no longer dominated by infectious diseases and epidemics, heart diseases and cancer account for 60% of all deaths over age 35,

followed by a rising toll from chronic pulmonary diseases.

What do all these dry statistics have to do with drug dependence? I have been speaking of quantity of life--not quality of life. Certainly, government programs of the past century including immunization, sanitation, regulation of water and food and drug supplies have contributed significantly to the increased quantity of life we enjoy. And, government has been successful in these programs because the average citizen could remain relatively passive. Of course, he and his family had to be immunized, the citizen had to support water and sewer systems through taxation, as well as food, drug, and occupational and environmental types of regulation. But it was not necessary for the citizen to undertake a life-long life style of exercising regularly, eating an appropriate diet, drinking alcohol in moderation or not at all and never driving when drunk, avoiding smoking by never starting or quitting if an individual had started, not abusing drugs, etc.

In addition to the spectacular hard drug abuse by the young -- which may be associated with criminal behavior -- there is to my mind an equally spectacular drug abuse by young, middle aged, and old alike in the field of tobacco, alcohol, and prescription and mood-altering drugs. As I reviewed the proceedings of your meetings of the past few years, it occurred to me that you should include tobacco as an appropriate subject to study and for an entire section or session at each of your annual meetings. Tobacco and other substances of abuse are inextricably intertwined; certainly, if the executive committees and program committees had individuals knowledgeable about tobacco use and abuse, then the sessions would follow. The tobacco and health field has been relatively neglected from the point of view of behavioral scientists; but in terms of overall public health problems, it certainly is as worthy of study by your group as is heroin or opium or marijuana. Clearly, our attitudes, mores. and concerns about the social acceptability of cigarette, pipe, and cigar smoking pervade the scientific world.

Saturday, June 14, 1980, the New York Times had an editorial complaining that unprecedented supplies of heroin were on their way to the United States while the Federal Government had cut funds for drug treatment programs and needed to get its drug policies in order.

Sunday, June 15, 1980, the Richmond Times Dispatch had an editorial on "Marijuana Hazards" pointing out that two national experts, who earlier dismissed warnings

about marijuana, now have joined a growing group of physicians and scientists who believe marijuana poses significant hazards to health.

The Richmond newspapers do not agree that smoking cigarettes presents health hazards sufficient for editorial comment. Perhaps that is appropriate, since Virginia (after North Carolina) produces more tobacco than any other state. From newspapers, television, radio, the halls of Congress in Washington, of state and even local legislatures, it is clear that our nation is concerned about heroin, other hard drugs, and marijuana, and our nation is willing to support biological, chemical, and sociophysiological studies on these drugs.

ADDITIONAL DATA ON CIGARETTE SMOKING

Approximately 53 million Americans are regular smokers while over thirty million have quit. Over 90% of cigarettes now have filter tips, compared with approximately 1% thirty years ago. In 1980 the average tar level as determined by the FTC is less than 15 mg compared with the 25-37 mg tar cigarette of the 1920s, 1930s, and 1940s. The nicotine level is approximately 0.8 - 1.2 mg per cigarette now compared to 2.0 to 2.7 mg nicotine 30 years ago. Nicotine may be the addicting chemical in the cigarette, but additional data will be necessary to prove the point. These recent data on relatively low tar and nicotine content cigarettes are for the first quarter of 1980, but give no information on carbon monoxide, HCN, nitrosamines, or other toxic or potential toxic compounds in cigarette smoke. Moreover, the data are for machine-smoked cigarettes in which the machine takes one 35 ml puff lasting two seconds per minute. An individual who takes bigger puffs or puffs more frequently, and inhales deeply and smokes to a shorter butt length may, in fact, switch as he is advised to do from a high tar, high nicotine cigarette to a low tar, low nicotine cigarette, and harm himself in the process, if he alters the way he smokes.

MORTALITY AND MORBIDITY FROM CIGARETTE SMOKING

There is a 70% excess mortality for all U.S. current male cigarette smokers.

Mortality ratios increase with the amount smoked (2 packs/day leads to an increased mortality ratio of 2.0 rather than 1.7). Mortality ratios increase with length of time smoked, age at which smoking began, and increase with depth of inhalation. For the ex-smoker mortality rates approach that of the non-smoker

by 7 to 10 years after quitting smoking and are essentially similar to that of the non-smoker after 15 years.

Cigarette smokers have a higher likelihood of developing either fatal or non-fatal myocardial infarction. Cigarette smokers have a higher incidence of being dead on arrival following a heart attack. Cigarette smokers have more aortic atherosclerosis, more atherosclerotic vascular diseases, and more arteriosclerotic aortic aneurysms. Women smokers also on the pill (birth control pills) have a marked synergism in their susceptibility, both to myocardial infarction and to subarachnoid hemorrhages.

Both men and women smokers have a higher incidence of cancer of the lung, oropharynx, larynx, esophagus, urinary bladder, and pancreas than do non-smokers. There is a dose response relationship between cancer development, tar content of cigarettes, years smoked, age smoking began, depth of inhalation, and certain types of occupations as well. Since women tended to smoke filter cigarettes, with lower tar and nicotine content, and since they appeared to smoke in what we described 10 years ago (for those who couldn't quit) as a less hazardous way of smoking -- fewer puffs, less inhalation, and leaving a bigger cigarette butt -- it had been thought that with women smoking the less hazardous product in a less hazardous way, perhaps their cancer incidence would be low. On the contrary -- over the past 5 to 10 years the rate of increase of lung cancer in women who smoke in this country shows a slope as steep as that for the lung cancer epidemic that occurred in men in the 1930s, 1940s, and 1950s and is now continuing in men, but at a less rapid rate of increase.

One can speculate that the female lung may be more susceptible to tobacco carcinogenesis. A few scientists are speculating that the female lung and trachea and bronchial tree is smaller than the male and may receive proportionately more of the carcinogens. But whatever the theory, there is an epidemic of lung cancer among smoking women.

Chronic obstructive pulmonary disease (COPD) in the elderly is extensively associated with long-term cigarette smoking. COPD incidence in both men and women is rising rapidly and has the beginning characteristics of the cigarette-induced lung cancer epidemic. Stopping smoking improves symptoms, but there is no evidence of anatomical healing of the lung.

In addition to these major diseases, smokers have significantly more disability days, more days of hospitalization without overt cancer, heart disease or COPD, than do non-smokers.

Among the highest risk group is the cigarette smoking pregnant female -- who even with low tar, low nicotine filter tip cigarettes continues:

to have babies who weigh an average 200 grams less and are shorter than non-smokers'babies,

to have a higher placental to birth weight,

to have a statistically significant higher spontaneous abortion rate,

to have higher perinatal mortality (as high as 100% greater for a high parity, public hospital status woman with previous low weight births, and/or anemia, if she is a heavy smoker). Perinatal mortality is approximately 10% higher in upper socioeconomic classes in women with few children, good nutrition, and good obstetrical care.

Clearly, what has been advertised as the less hazardous cigarette of the late 70s is still hazardous.

Smoking in this country appears to be class related as has been clearly demonstrated in the United Kingdom. However, young girls are beginning to smoke at rates equal to those of young boys in the 9 to 17 year group.

THE QUIT RATE

Many Americans have received and acted on the health message that physicians and scientists have communicated to the American people.

Smoking Statistics in the United States

White male	51.5% smokers in 1965	to 36.3% smokers in 1979
Black male	60.8% smokers in 1965	to 42 % smokers in 1979
White female	34.2% smokers in 1965	to 28.2% smokers in 1979
Black female	34.4% smokers in 1965	to 28.9% smokers in 1979

Current data in the United States shows smoking among adults at 32.3% overall, the lowest level in 45 years. In contrast, in the depression year of 1935, Fortune magazine estimated 37.3% of all adults smoked.

WHAT IS THE ROLE OF GOVERNMENT?

Certainly, if tobacco-containing cigarettes were developed by a major pharmaceutical manufacturer today as a vehicle for delivering nicotine or carbon monoxide or some other chemical to the human lung, it is unlikely that tobacco-containing cigarettes would be approved by the FDA.

As matters stand, cigarettes are neither a food nor a drug and are not subject to regulation by an governmental department, except with respect to advertising, through the FTC.

My own view is that the government's role is to educate children and adults about tobacco's hazards, and further, to do research on the pathophysiology of the multiple disease processes caused by the over 4800 different chemicals identified in cigarette smoke.

Where people in a work setting wish pure air, it seems to me a cooperative arrangement between non-smoking employees, smoking employees, and/or employer should be worked out. Failing this, government may need to step in to protect the rights of the non-smoker, assuming, of course, appropriate legislation is on the books.

THE ROLE OF PRIVATE GROUPS OF RESEARCH SCIENTISTS

The use or abuse of hard drugs including excess acute alcohol ingestion leads to immediate and frightening effects, especially when violent crimes become part of the drug scene. I am concerned about heroin, opium, cocaine, marijuana, alcohol, the amphetamines, and related drugs, just as you are. I am concerned about the wrecked young lives and the enormous cost to society.

While the number of heroin and opium abusers is far fewer than the 5% of our population estimated to be alcoholics, I remain puzzled why cigarette smoking, which every year causes 225,000 excess deaths from cardiovascular diseases, 102,000 excess deaths from cancer and 19,000 excess deaths from pulmonary disease (not to mention deaths from fires accidentally set by burning cigarettes)-- I repeat -- I remain puzzled why more behavioral scientists are not interested in this phenomenon. Is it because cigarette smoking was socially acceptable just a few years ago? Is it because most of you are ex-smokers, or still smoke, or because your boss or your spouse or your parents smoke? Is it because there is no career path for behavioral scientists interested in the tobacco problem?

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I think all of the above may be true. Very few dollars are available from the National Institutes of Health, the United States Government, The Department of Health and Human Services, the Office on Smoking and Health, National Institute of Mental Health, or any other governmental agency to study this problem in a comprehensive manner and with support reasonably well guaranteed over a long period of time assuming the work is well done.

Perhaps a group such as yours with support from a wide variety of sources can provide the stimulus -- act as the catalyst for improving both the quantity and quality of research in the behavioral sciences regarding smoking as a form of drug dependence. I know your response -- there aren't any good ideas. My response would be to point to a number of major scientific fields where significant available research support stimulated research, such as in cancer chemotherapy. The exploding existing field of psychopharmacology may be similar, although the ideas may have preceded the funds. If scientists don't ask. the questions, it's unlikely they'll find the answers.

In the last few years, the National Cancer Institute, Office on Smoking and Health, and American Cancer Society convened groups to review the latest data on behavioral aspects of tobacco related research and all are in agreement that the field is underpopulated and needs nurture from senior scientists and organizations concerned with both health research and education.

SUMMARY

Much progress has been achieved over the past twenty years in informing the American people of the hazards of cigarette smoking. Over thirty million Americans have quit smoking cigarettes; many have quit as a result of social pressure-- cigarette smoking becoming less socially acceptable. The average cigarette has less than half as much tar and less than half as much nicotine as its predecessor cigarettes a quarter century ago. Moreover, most American cigarettes today are filtered.

We still do not know why people begin or why they continue to smoke. I would urge the Committee on Problems of Drug Dependence to add tobacco -- as you've added alcohol -- to your agenda for research, for cooperative studies, and for an annual update. You should examine and speculate upon the reasons why 53,000,000 Americans' dependence on tobacco has attracted so little attention from scientists with

knowledge and expertise such as yours. And when you have the answers, I hope you will utilize those answers to attract more research and appropriate action to our number one public health problem and our number one drug dependence problem.

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Governmental Control of Individual Behavior—Philosophical and Practical Considerations

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THE UNIVERSALITY OF RESTRICTIONS

Since the Second World War, perhaps more than at any other time in our history, our society has engaged in continuous and often heated debate about the right of governments to restrict individual freedom in matters of taste, beliefs, personal practises, and choice of pleasures and entertainments. This is well illustrated by, though by no means restricted to, the use of cannabis, cocaine and other drugs. The arguments about these are reminiscent of the debates about alcohol half a century ago. Then, as now, the fundamental legal and philosophical issue has been to what degree a government has the right or justification to limit the freedom of individual citizens to live their private lives as they wish.

It is a fact of life that all societies impose many kinds of restriction on the freedom of individual citizens. In contemporary industrialized societies, in which the debate is perhaps the most vocal and audible, we tend to think in terms of restrictions imposed by governments. Indeed, restrictions are imposed by all levels of government, and in all spheres of human activity. In the United States and Canada, for example, the federal governments restrict our freedom to spend our personal income as we choose, by levying income taxes which they redirect to various social purposes with which we may or may not agree. The military draft restricts our freedom to serve or not serve in the armed forces as we might choose. The criminal code determines whether we will or will not have the freedom to read certain books or magazines, view certain films, and use certain drugs for pleasure as distinct from medical therapy. At the state or provincial level, governments determine how rapidly or slowly we may drive our cars on the highway, what forms of education our children may get, whether we must or must not join a collective bargaining unit, and so forth. At the municipal level, local governments determine in what areas of the city we may build, and whether we may do so in the style and for the purpose that we choose, whether we may or may not shop on Sunday, how we may dress in certain locations and at certain times, and so forth. The list is endless. There is a tendency for us to feel that this re-

presents a progressively greater modern invasion by government into the freedom of the individual, and many people long for the earlier days in which our forebears supposedly lived according to their own ideals and wishes, and in which their homes were their castles.

Unfortunately this nostalgic yearning for freer days of yore is based on a delusion. Earlier, and even primitive, societies have, or had, equivalent restrictions imposed by the society upon the individual, even though these restrictions were of a different nature. In our own society, one does not have to look back too many decades or centuries to see such astonishing examples as obligatory Sunday closure of all businesses, the prohibition of contraception, and even the prohibition of bathtubs and bathing of the whole body in the nude except for medical reasons. In primitive societies, the restrictions are probably even greater in importance because the range of possible activities is much smaller, and each prohibition weighs more heavily. The descriptions given by anthropologists reveal the gravity with which religious taboos and tribal rituals were enforced.

One must conclude, therefore, that restriction of individual freedom is part of the price for living in an society. In order that a large number of people may live together in reasonable cooperation and harmony, enjoying the benefits of mutual help and protection, it seems necessary for each member of the group to give up certain freedoms for the sake of maintaining the necessary unity. Our society is probably in many senses more free than most others in human history. Nevertheless, the restrictions on individual behavior are real enough to warrant some examination of the basis on which they are formulated. Moreover, some of them are now resented by enough people to warrant consideration of their purpose and validity.

REASONS FOR UNIVERSALITY OF RESTRICTIONS

Though they may seem at times to be arbitrary and capricious, limitations imposed by a society upon the behavior of its individual members are usually not deliberately malicious. Of course, one must exclude from this statement the cruel and perverse limitations that have sometimes been imposed by despots. In the remarks that follow, the assumption is made that we are referring to a fundamentally democratic society.

Social restrictions on individual behavior usually represent an attempt to achieve the greatest common good, as this is perceived at the time the rules are made. In earlier days, when travel and communications were far below their present levels and xenophobia was the norm, homogeneity of any given society was evidently a highly desirable attribute. The more values, beliefs and customs that people shared, the easier it was for them to accept and cooperate with each other. Therefore, the Sunday blue laws were accepted by most people in North America as a perfectly justifiable and reasonable means of ensuring universal adherence to the predominant puritanical version of Christianity. In our own time,

obligatory chlorination or fluoridation of municipal water supplies is seen by most citizens not as an infringement of personal freedom to drink water of a different taste, whether contaminated or otherwise, but as a reasonable means of serving the common good by minimizing the health costs of typhoid fever, dysentery, and dental caries.

In general, it is probably fair to say that such social restrictions of individual behavior are conscious or unconscious weighings of the individual's freedom versus the interests of the larger group. In general, they depend upon an explicit or implicit weighing of the costs versus the benefits of any given behavior to the individual and to the society at large.

COSTS AND BENEFITS OF DRUG USE AND DRUG CONTROL MEASURES

The question of drug control measures offers a good example of the various considerations that go into the formulation of social policies with respect to individual behavior. They illustrate very well the scope and complexity of the cost-benefit analysis that must ultimately serve as the justification for any specific policy. It is useful to analyze the nature of the costs and benefits that must be weighed.

In the case of licit drugs used for medical or other therapeutic purposes, the nature of the costs and benefits, and the balance that is drawn between them, are relatively simple. The major benefit is obviously the relief of disease and suffering, though one must not ignore the significant economic benefit that comes from the creation of a pharmaceutical industry which provides employment, profit, and taxation revenue. The major costs can be identified as the risk of iatrogenic disease created by improper use of the drugs, and the economic burden to the individual and to the society, as a result of widespread and sometimes unnecessary use of newer and more expensive agents.

When we consider the nonmedical use of licit and socially approved substances, such as alcohol, caffeine, and tobacco, the spectrum of costs and benefits is rather different. The most important benefit is individual pleasure, although this can often be a socially shared pleasure which reinforces group values and traditions. This is particularly true of the long established role of alcohol in the social practices and traditions of our society. A very important additional benefit is the large economic contribution made by the production, distribution and taxation of these commodities. The costs are most typically seen or incurred at high levels of use, and are of three major types. The first category includes the consequences of acute excess, such as alcohol-related motor vehicle accidents, violence, rowdiness, and other behaviors which infringe upon the rights and tranquility of other people. The second broad category includes the harmful effects of such agents upon the health of the user. Alcohol-related diseases of the liver, nervous system, or cardiovascular system, and bronchopulmonary disease caused by heavy smoking, are examples of major costs to the individual, the

family and society at large, in the form of both personal suffering and economic costs to the health care system. A third category of costs, both social and economic, is represented by lost productivity, disruption of families and associated welfare costs, an the creation of special problem groups such as the skidrow cultures in many large cities.

In relation to the nonmedical use of illicit drugs, certain additional factors must be considered. The spectrum of "benefits" becomes much more variably defined, and depends much more on whose point of view is reflected in the definition. For example, the euphoria induced by amphetamine, or the alterations of perception produced by LSD, are perceived by the users as novel, interesting, and hence desirable, while to the general public all such drug use appears bad - at best escapism, or at worst dehumanizing. The life style of the chronic heavy user of cannabis is often represented by the user as relaxed and more human by virtue of its avoidance of the competitiveness of conventional society; in contrast, the same user is often seen by the majority of the public as devoid of ambition, shiftless, and irresponsible. In general, the heavy users of such drugs perceive the effects as beneficial in providing interest and solace to their lives, while society at large sees the drug use as a threat to its values. In addition, a major cost of such drug use arises from its illegal status, and consists not only of the economic cost of law enforcement measures against the use and sale of the drugs, and the loss of currency from the country for the illict importation of some of them, but also the human costs to users who are convicted and imprisoned on charges of possession or trafficking.

It is worth noting here that the possible conventional therapeutic benefits of a drug are quite irrelevant to the legal status of its non-medical use. For example, the possible value of cannabis as an anti-nauseant agent, or in the treatment of wide-angle glaucoma, has no real bearing on the cost-benefit balance concerning legal controls of the non-medical use of cannabis for personal pleasure. This is readily apparent from our attitudes and practices with respect to opiates. The therapeutic use of morphine is perfectly legal, while trafficking and possession for non-medical use are illegal. In fact, the prohibition of manufacture and importation of heroin for therapeutic use, in an effort to decrease availability for non-medical use, is seen by many physicians as a glaring anomaly that illustrates the fallacy of confusing the two.

RELATION TO LEVELS AND DISTRIBUTION OF CONSUMPTION

In general, the perceived benefits of the use of licit drugs, and even those of illicit ones, tend to occur at the relatively low levels of use that are characteristic of the occasional or social user. In contrast, the harmful effects on health and behavior, and most of the economic costs, tend to occur in association with heavy use.

There is now a considerable body of evidence to demonstrate that the range of levels of drug use by individual users in a population

follows a unimodal distribution-of-consumption curve that does not differentiate, by any sharp inflection, between the normal and abnormal, light and heavy, social and addicted users. Rather, there is a single continuous smooth transition between a majority of light users and a minority of very heavy users, The levels of hazard associated with the various risks mentioned above tend to rise progressively with increasing average daily individual consumption. Consequently, government interventions which are aimed at reducing individual and social hazard by decreasing the levels of drug consumption tend to affect both light and heavy users alike.

This is illustrated well by the effects of price manipulations and of changes in legal status that have been tried at various times in various countries. For example, when alcohol was rationed strictly in France under the German occupation, the death rate from alcoholic cirrhosis in Paris fell rapidly and drastically, only to rise equally rapidly after liberation in 1944. The enactment of prohibition in the United States began with a variety of legal restrictions imposed by the States and by the Federal government on interstate commerce in alcohol in 1916, and continued with the constitutional amendment enacted in 1921. These measures were followed by an abrupt and rapid fall in the death rate from alcoholic cirrhosis in the United States. Following repeal in 1932 the death rate did not rise nearly as rapidly as it had fallen, because the United States was now in the depth of the Great Depression, and the cost of alcohol relative to average individual earning capacity had risen sharply. Similar studies from Canada have shown a similar marked effect of price interventions on the death rate from liver cirrhosis, and in Trinidad, price changes had equally striking effects on the rate of alcohol-related road vehicle accidents.

It is clear, therefore, that government interventions can effectively modify individual behavior with respect to alcohol and drugs, even the behavior of those whom we would consider to be addicted and at maximum risk of the health hazards associated with addiction. The questions that must be asked are not whether such interventions can work, but rather, at what cost, for whose benefit, by what methods, and to what degree? The objective of such interventions is obviously to keep the level of use low enough to minimize the individual and social costs of drug use, while either maximizing the pleasure or interfering with it as little as possible. However, a further objective should be to keep the cost of the intervention itself as low as possible.

BALANCING COSTS AND BENEFITS

The task of balancing the costs versus the benefits is considerably more complex than might at first appear. It actually involves at least three different types of cost-benefit accounting. The first is a balancing of the costs versus the benefits of drug use at any given average level of use by the whole population. How much pleasure from drug use is worth how much risk of physical or social harm to the heavy users, or of health and economic costs to the community at large? The second cost-benefit accounting must be

applied to the various types of governmental intervention or control measure which might be applied. For example, deliberate price manipulation by elevation of taxes on alcohol or tobacco is most likely to decrease the level of use sharply if the prices are raised drastically. But the same intervention may result in a net fall in revenue to the government if it is too effective. The third and most difficult type of cost-benefit accounting involves a comparison of the costs and benefits of uncontrolled use with the costs and benefits of the control measures taken to prevent this. The difficulty here lies in the fact that one is not comparing the costs and benefits of the control measures against the costs and benefits of the actual level of use found while these measures are in force, but rather, one must compare the costs and benefits of the control measures with those of the situation that would probably exist if the control measures were not in place. Experience shows, for example, that reduction of the legal drinking age is associated with a large increase in the level of consumption of alcohol by teenagers, and a disproportionate increase in the number of alcohol-related traffic accidents among this age group. A particularly vexing problem is to assess how much increase in teenage drinking, drunkenness, and drinking-driving accidents, is an acceptable price to pay for the legal and philosophical consistency that someone who is old enough to be conscripted for military service or to vote should also be entitled to drink legally.

INPUTS TO DECISION-MAKING

It will be obvious from the examples given above that the drawing of such a cost-benefit balance involves at least three different types of input. The first and in some ways easiest input is that of accurate factual information. Objective research can demonstrate what the consequences of a given level of intake of a particular drug may be, and also what individual and social consequences may follow from a particular social policy. Disagreement among scientists at this level are, on the whole, found at the fringes of knowledge, at which facts are still not yet firmly established. Such differences of opinion concerning actual fact are relatively easy to identify, and the methods for resolving them are part of the objective equipment of science.

The second type of input is the estimation of probability of occurrence of any particular type of consequence at any given level of drug intake, or similarly the estimation of probability of occurrence of any particular individual or social consequence of a particular policy option. Here, the reliability of estimates rests upon the degree of expertise and impartiality of the experts making them. In general, this is recognized as another part of the function of the expert. Subjective feelings, wishes and biases may all influence the estimate of probability, but scientists by training should be relatively capable of separating their personal preferences from their estimates of probability.

The third type of input is totally different in nature, and consists of the value judgment concerning the relative weights to be attached

to the different costs and benefits. Clearly, the importance of any particular consequence depends on the scale of values of the individual making the judgment. This is easily grasped by comparison with similar problems in other fields. Two internationally acclaimed experts in nuclear physics can disagree radically concerning the desirability or undesirability of a particular nuclear arms program or nuclear energy program. The difference does not depend upon substantive disagreement concerning the nature of radiation effects, or the probabilities of their occurrence at any given level of radiation, but upon such considerations as whether it is better to be dead than red or better to be red than dead.

When one reaches this level of evaluation, dependent upon the religious, philosophical and cultural backgrounds of the people making the judgments, it is apparent that an expert in nuclear physics, or an expert in psychopharmacology, has no particular claim to moral superiority over the ordinary citizen. When it comes to making a value judgment concerning the future nature and course of our society, every citizen is entitled to the same consideration with respect to his or her scale of values. The expert is expert only in matters of scientific fact and probability estimate. Once he has explained the facts and probabilities, his personal preferences and values have no more weight or authority than those of every other citizen.

Since the government represents the ordinary citizens in a democracy, it is not surprising to find that governments tend to follow, rather than lead, public attitudes and opinions in matters which are heavily dependent upon moral, religious, and cultural values. In matters such as drug control legislation and its enforcement, governments and political parties are as divided within themselves as the general public is. This is not necessarily an unhealthy state of affairs, because it puts the onus clearly back where it belongs, on the shoulders of the public at large. Our function as scientists is to explain, but it is the function of the public to decide on its values.

When viewed in this light, the role of government intervention in individual behavior is really that of codifying and formalizing the beliefs and values of the constituents whom the government represents. In drug controls, as in any other matter within the purview of government, it is unrealistic to hope for unanimity. That some measures are unpopular with some segments of the citizenry is almost inevitable. Under these circumstances, drug control measures are philosophically no more unjust than any other legislation which does not have the unanimous backing of the entire population. If the citizenry at large wish that a certain field of human activity should lie entirely within individual discretion, or conversely that it be subject to governmental intervention for the common good, it is the responsibility of the citizens to make that known to their elected representatives. Viewed in this light, the role of personal choice is not merely to use or not use a drug, but to participate in choosing the type of society we wish to live in.

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Compliance and Enforcement Programs of the Drug Enforcement Administration

R. W. Buzzeo

It is indeed a pleasure and an honor to be with you at this your 42nd Annual Scientific Meeting of the Committee on Problems of Drug Dependence, Inc., and to represent Mr. Peter B. Bensinger, Administrator of the Drug Enforcement Administration,

I want to emphasize that DEA considers it absolutely essential to establish and maintain a close relationship with organizations such as this. The membership which you represent forms a vital partnership with DEA in monitoring over 600,000 registrants, both practitioner and nonpractitioner.

Our sincere desire is to remain approachable and responsive to the needs of these many registrants. Little progress would be made if the DEA were to remain aloof, issuing edicts, regulations and policies from Washington. We need to monitor the registrants and we need to work closely with all groups in preventing diversion. We must understand that enforcement or medical programs going off in separate directions is a simplistic approach -- we need to work together in addressing a common problem.

I would like to highlight briefly with you today the Drug Enforcement Administration and its Compliance and Enforcement Programs, which include DEA activities in State-Federal cooperation and with professional licensing boards, and then close with a major problem which faces this country.

The DEA is the lead Federal law enforcement agency charged with combatting drug abuse and the drug traffic. We have both an enforcement and a prevention responsibility.

The Controlled Substances Act of 1970, which we enforce, is designed to improve the administration and regulation of manufacturing, distribution, and the dispensing of controlled substances by providing a "closed" system for legitimate

handlers of these drugs. The idea of a closed system, through which flow 20,000 brand named products controlled under our current law, is to reduce the widespread diversion of these drugs from legitimate channels into the illicit market.

Often the public associates DEA with its better known role of criminal drug investigation. The resultant arrests and seizures of illicit drugs make daily headlines around the nation.

Perhaps less colorful, but no less important, is our compliance work in which we enforce those portions of the Controlled Substances Act that apply to the manufacturers, distributors, prescribers, and dispensers.

The DEA has about 4,200 employees worldwide -- most of them operating under five regional offices in the United States.

Approximately 2,000 of our employees are Special Agents, and about 200 are Compliance Investigators. These 200 investigators, working closely with 7,000 State investigators, are responsible for monitoring a market which, for comparison, is reached by some 26,000 medical service representatives of the pharmaceutical industry.

DEA's regulatory mission is performed by its Office of Compliance and Regulatory Affairs. Under it, we carry out such major responsibilities as registration, import and export monitoring, voluntary compliance, scheduling, quotas, regulatory investigations, State assistance programs, pharmacy theft prevention, DAWN, and the ARCOS system, which helps us spot problems and abuses in the distribution of controlled substances.

Our Compliance Program is concerned with the registrant who criminally diverts controlled substances into the illicit market. Although these are in the minority, the damage resulting to our society from such diversion can be most serious. These criminal diverters are no better than the individual who deals in heroin; even worse, since they have abused the trust placed in them by society.

Diversion has been reduced at the manufacturer/distributor level as a direct result of regulatory requirements under the Controlled Substances Act and Federal and State efforts. I am sorry to say the same results have not been achieved at the practitioner level, which includes physicians, pharmacies, researchers, hospitals, and clinics. Currently, the sources of diversion at this level are forged prescriptions, indiscriminate prescribing, thefts, and illegal sales. We estimate that 300 million dosage units are diverted annually, with 70 to 90 percent coming from the retail level. Primary responsibility at this level falls to, the States under the Controlled Substances Act which requires DEA to register every professional who possesses a valid State license unless he has. a drug felony conviction or materially falsifies his registration application.

It is entirely true that only a minority of practitioners are deliberately engaged in drug diversion; however, this minority can, and does, create serious drug problems in many parts of the country. In light of this problem, DEA embarked on a program called "Operation Script," a cooperative effort which combines the resources of both DEA and State drug agencies, which targeted 94 preselected pharmacies (44) and physicians (50) in 22 States for extensive investigation.

This increase in effort has focused DEA technical, investigative and legal expertise against preselected retail violators to produce high impact investigations.

This increase in effort will be valuable in:

(1) decreasing diversion,
(2) demonstrating the Federal Government's concern,
(3) increasing public awareness of the diversion and abuse of legitimately manufactured controlled substances,
(4) encouraging States to address practitioner diversion,
(5) demonstrating the need for additional and continuing Diversion Investigative Units (DIU's),
(6) giving impetus to potential Federal legislation,
(7) supporting possible FDA actions regarding indications and uses of controlled substances,
(8) obtaining information which may be utilized in decreasing quotas and/or restricting imports.

At this point, indictments have been returned in seven of these cases and fifteen more are pending. Eight convictions have already been obtained for the illegal sale of controlled substances.

These eight (two pharmacists and six physicians) were responsible for an estimated diversion of 15.4 million d.u. per year.

Clearly, with 600,000 practitioners and only 2,000 agents/investigators, we must concentrate our efforts on practitioners who are strongly suspected of criminality.

For example, in FY '79, as part of our regular Compliance and Enforcement Investigative Program we were able to conduct only 129 practitioner complaint investigations (62 pharmacists, 42 practitioners and 25 others), while DEA arrested 4,900 nonprofessionals.

As part of our State assistance, we have developed a State criminal investigation operation aimed at prosecuting willful retail registrant diverters. We call it the Diversion Investigative Unit Program. DEA supports these State-run, State-manned units by providing 18- to 24-month seed funding, regulatory training, a full-time DEA representative working in the unit and investigative support. In addition to the DEA representative, the unit and its overseeing policy board are composed of personnel from the State's various regulatory

boards and its law enforcement agencies. This blend of expertise and the flexibility provided have had a beneficial impact in the nineteen States (Massachusetts, New Hampshire, New Jersey, North Carolina, Georgia, Hawaii, Washington, Oklahoma, Michigan, Pennsylvania, Nevada, Illinois, Texas, California, Alabama, Maine, Arkansas, Utah, New Mexico and the District of Columbia) where the units now exist. Perhaps the best measure of the DIU Program's success has been the willingness of State governments to continue these units with State funding.

Since the program's inception in 1972, these DIU's have accounted for approximately 3,000 arrests. In Calendar Year '79, these units made 450 arrests, including 170 registrants and removed 750,000 dosage units of controlled substances from the illicit market.

A spin-off of the DIU Program is our application of computer technology to identify problem drugs and problem registrants for investigation. In a pilot program in San Francisco, we utilized our Drug Abuse Warning Network (DAWN) to identify legitimate drugs appearing most frequently in the hands of abusers and our Automation of Reports and Consolidated Orders System (ARCOS) to pinpoint registrants excessively purchasing these drugs. This project, in conjunction with the California DIU, resulted in the criminal indictment of nine physicians and civil actions directed toward 21 pharmacies, with administrative actions against an additional 10 physicians and 16 pharmacies.

Additional progress in curbing diversion at the retail level has been made with the development and implementation of a program to address pharmacy thefts. Thefts from pharmacies and practitioners accounted for the loss of over 34 million (out of 43 million) dosage units of controlled substances in 1978, and in 1979 a projected 40 million (out of 52 million) dosage units. I might add that retail pharmacies are subjected to theft more than any other pharmaceutical business category. In the first six months of 1979, 73.5 percent of all thefts reported to DEA were reported by pharmacies. During this same time period 64.4 percent of all controlled substances diverted by theft were stolen from pharmacies.

In order to assist pharmacists who are concerned about this alarming increase in pharmacy thefts, the DEA initiated a Pharmacy Theft Prevention (PTP) Program which is available to all communities. DEA's PTP Program is a community action approach to pharmacy theft.

The nucleus of a PTP Program is the leadership in a community. These leaders form an executive committee which includes representatives from the police department, DEA and the professional associations.

The DEA currently has eleven active PTP cities and three that are in the developmental stages. The active programs are:

Philadelphia Pennsylvania; Milwaukee, Wisconsin; Nashville, Tennessee; Johnson County Kansas; Dallas, Texas; Denver, Colorado; Seattle, Washington; San Diego, California; Rhode Island State; Utah State; and Clark County, Nevada. Programs are developing in Louisville, Kentucky; San Juan, Puerto Rico; and Pittsburgh, Pennsylvania.

In addition, DEA has been working with the various medical associations in developing prescribing guidelines that provide and establish acceptable professional responses to guard against contribution to drug abuse through indiscriminate prescribing of drugs or the acquiescence by practitioners to unwarranted demands of some patients. These guidelines will also work to ensure that multiple prescription orders are not being obtained by the patient from different physicians, that prescriptions only provide enough of a drug to carry the patient to his next scheduled appointment, and that prescriptions are alteration-proof.

While progress is being made, the curbing of retail diversion in the future will require substantial increases in State and professional monitoring of practitioners in order to identify the problem areas and to develop solutions.

Before I discuss a major area of concern, I first wish to address some additional items of interest --

Dextropropoxyphene

Pursuant to a recent UN decision to add dextropropoxyphene to Schedule II, the DEA has determined that the placing of bulk dextropropoxyphene into Schedule II and the leaving of all dosage units in Schedule IV will meet our international obligation as required by the Single Convention and our domestic needs. In addition, a recent recommendation by FDA that propoxyphene be classified as a narcotic will require practitioners using dextro-propoxyphene in maintenance or detoxification programs to register as NTP's.

Clandestine Laboratories

Another area of interest is DEA's Clandestine Laboratory seizures. In 1979, 237 labs were seized in the U.S. This includes 10 amphetamine producing labs; 137 methamphetamine and 53 PCP labs. Already for the first quarter of 1980, 74 labs have been seized. This figure is 31 percent of all labs removed last year.

International Diversion

Another major drug abuse concern of the DEA is the diversion of legitimate pharmaceuticals from international commerce. Many of the manufacturers of pharmaceuticals are located in Europe, where regulatory controls are quite different from those of the

United States. Several drugs, such as methaqualone, secobarbital and methamphetamine, which are tightly controlled in the U.S. because of high abuse levels, have not historically been considered a problem in some European countries and therefore have not been or have only recently been controlled. These conditions afford drug traffickers opportunity for diversion. Using various means of ordering and employing complex shipping routes, drug traffickers are diverting large quantities of drugs of abuse.

In response to this growing U.S. and potential worldwide problem, the DEA has initiated a program in cooperation with host governments to establish a voluntary program of soliciting cooperation from various manufacturers and pharmaceutical firms in Europe. Firms are encouraged to watch for and report unusual or suspicious orders from customers, requests for unusual or suspicious labeling or shipping instructions, and excessive orders.

It appears the long-range solution to this problem of drug diversion from legitimate sources will require the enactment of additional legal controls over nonnarcotic controlled substances. Additionally, it is necessary to ensure the application of adequate criminal or civil penalties to those firms or individuals that violate legal requirements.

Only through extensive international cooperation and sharing of information can countries effectively curtail the illegal international movement of abusable pharmaceuticals.

Southwest Asian Heroin

In many respects, DEA has seen considerable progress in its efforts, but the instabilities of the governments of Southwest Asia are having a dramatic adverse impact on the dimensions of the world drug situation. This area -- Iran, Afghanistan, and Pakistan -- is capable of producing many times over the amount of opium needed to satisfy world demand. This gives us cause for concern. The consequences of excessive opium production there have already been experienced in Europe, and now are being felt in the United States as well.

It is estimated that in 1978 Afghanistan produced 300 metric tons of opium and Pakistan produced approximately 400 metric tons, for a regional total of about 700 metric tons. Iran cannot be included in the 1978 total because at that time opium cultivation in Iran was legal and controlled. In 1979, however, opium production in all three of these countries in Southwest Asia is believed to have increased to a maximum of 1,600 metric tons.

We estimate a regional consumption of 1,000 metric tons of opium, leaving 60 metric tons of heroin available for worldwide distribution from this one area of the world.

Of course, these are "guesstimates." As you can well imagine, intelligence-gathering in that part of the world is, at best, very difficult. Our agents stationed abroad are our primary intelligence

source. However, DEA has had to close its offices in Iran and Afghanistan. Our efforts in Pakistan have been disrupted extensively, and still have not returned to the levels of previous years.

Foreign governments are often a secondary intelligence source, but we do not have ongoing enforcement and intelligence exchange in Iran and Afghanistan, and these countries have lost a number of their career drug law enforcement officials.

The high quality and availability of Southwest Asian heroin has made it a very marketable commodity. By mid-1977, West Germany was inundated with this high-quality Southwest Asian heroin. The problem has since spread to other West European markets which traditionally have been and continue to be outlets for Southeast Asian heroin. Despite sincere attempts by European governments to control the narcotics addiction problem, the situation has continued to worsen.

Throughout 1979, Western Europe served as a "sponge," absorbing the increased Southwest Asian heroin production. Approximately 2.5 metric tons of heroin were consumed in Western Europe that year. By way of contrast, a recent intelligence study estimates that in 1978 0.6-0.8 metric tons of Southwest Asian heroin, representing 17 percent of the total market, entered the United States. I expect that proportion to have doubled during 1979.

Although the heroin picture in Western Europe may be stabilizing, the situation still is not good. Drug-overdose deaths in West Germany, for example, are almost double those of this country and yet their population is one-fourth of ours. In West Germany, street-level purity is currently between 20 and 40 percent and prices in some European cities have dropped to as low as $25,000-$35,000 per kilogram. According to our latest figures, that same kilogram would sell for about six times as much in New York City.

DEA intelligence reflects that some Iranian citizens, unable to move cash out of that country because of the currency regulations, have "converted" their cash to narcotics and have smuggled their assets out in that fashion. The profit motive has enticed numerous black, Hispanic, Italian, Iranian and other traffickers to enter the Southwest Asian heroin trade in the United States. Although at present this trade is best characterized as fragmented, there are indications that in the future it will be dominated increasingly by cohesive criminal groups.

Over the past two years, there has been a rising number of seizures and resulting investigations. During 1977 and 1978, small quantities of Southwest Asian heroin appeared in the U.S. and were confined to the New York/Washington, D. C. corridor. Since then, undercover purchases of Southwest Asian heroin also have been made in Chicago, Detroit, San Francisco and Los Angeles.

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Seizures of heroin in this quantity and purity have not been experienced in several years.

Given the magnitude of recent developments, the question then becomes, "What plans are there for coping with this new presence and accelerating problem?" Unfortunately, there are no easy answers.

The United States Government has developed initiatives to attack the Southwest Asian heroin problem. The Administration is making the Southwest Asian heroin effort a high priority and is coordinating efforts of the Departments of Justice, State, Treasury, Defense, and Health and Human Services.

The Department of State is seeking international cooperation, not only through contacts with individual nations, but also by raising the issue in international forums such as NATO. We are accelerating the enforcement activities of the U.S. Customs Service and DEA both in the U.S. and abroad. Additionally, New York, Philadelphia, Boston, Newark, Baltimore and Washington are being designated target cities where major efforts are needed most to fight the flow of Southwest Asian heroin. The State and local law enforcement agencies are being involved in the antiheroin effort to the maximum extent. As you can see, the Drug Enforcement Administration is involved in the forefront of this action plan.

On February 28, 1980, President Carter and Attorney General Civiletti hosted approximately 120 law enforcement officials including all State attorneys general and several police chiefs and prosecutors. At this meeting, a five-point program to address the threat of Southwest Asian heroin was discussed with these enforcement officials and their cooperation and participation were encouraged.

Both Attorney General Civiletti and Mr. Bensinger have met with the Italian Prime Minister and Minister of the Interior of the Federal Republic of Germany to discuss mutual concerns regarding the Southwest Asian heroin problem. We intend to continue to assist foreign law enforcement agencies with support services directed at identifying and immobilizing major drug trafficking networks.

In all cases, our preference is to work as close to the source as possible; but, in the case of Southwest Asia, that door has virtually been slammed shut. Consequently, we have accelerated our efforts as close to the source as we can get -- through our agents and country attaches stationed along the transshipment and destination corridor in Western Europe.

DEA has recently established a Special Action Office/Southwest Asian Heroin to meet the imposing threat of renewed heroin production, transshipment and trafficking in and from Europe, the Middle East, and parts of Southwest Asia's opium producing countries.

SAO/SWA will address this serious situation on both the European and North American continents in a coordinated, directed, high-priority enforcement effort.

All of these actions are designed to counter the increasing availability that could cause Southwest Asian heroin to reach epidemic proportions. We believe that for the present our initial measures will blunt this threat to the best extent possible.

In closing, let me leave you with the following thoughts. The DEA is committed to preventing diversion. However, you, too, must be conscious of your responsibilities in the fight against drug diversion and abuse.

I am confident that the application of your know-how and resources to the abuse problem will have significant results. The urgent need to effectively curtail drug abuse and prevent diversion cannot be overemphasized. DEA has assigned the problem a high national priority. You can help by giving your utmost attention to the abuse of controlled substances.

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Reinforcing Properties of Buprenorphine: A Behavioral Analysis

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Buprenorphine, a partial agonist of the morphine type, is a congener of the narcotic agonist etorphine, and the antagonist, diprenorphine (Lewis 1974). Buprenorphine has morphine-like analgesic, subjective and physiological effects and its analgesic potency is estimated to be 25 to 40 times that of morphine (Cowan et al. 1977, Jasinski et al. 1978, Houde 1979). However, buprenorphine does not produce significant physical dependence in man (Jasinski et al. 1978, Mello & Mendelson 1980). The antagonistic potency of buprenorphine is equivalent to that of naloxone but it has a longer duration of antagonistic action, comparable to that of naltrexone (Jasinski et al. 1978).

Buprenorphine (8 mg/day) significantly suppressed heroin self-administration (21 to 40.5 mg/day) by heroin addicts over 10 days ($P < .001$) in comparison to buprenorphine placebo (Mello & Mendelson 1980). Placebo control subjects took between 93 and 100 percent of all the heroin available. Subjects liked buprenorphine and said they would prefer it to methadone or naltrexone. In view of buprenorphine's safety, efficacy, and acceptability to heroin addicts, it should be an effective pharmacotherapy for heroin addiction.

This study examines the potential abuse liability of buprenorphine in a primate drug self-administration model. This model has proved useful for the preclinical assessment of drug abuse liability and it is generally agreed that most drugs abused by man are also self-administered by monkey (Schuster & Johanson 1974, Thompson & Unna 1977, Griffiths et al. 1980). This report is the first of a series of studies that examine the conditions under which buprenorphine is reinforcing, i.e. will maintain operant behavior leading to its intravenous administration in monkey. Woods (1977) has shown that substitution of buprenorphine (.0001-.10 mg/kg/inj) for codeine (.3 mg/kg/inj) maintains responding on an FR 30 schedule of reinforcement, but response rates were lower than for codeine, morphine or heroin. Evaluation of relative reinforcing efficacy is difficult because of the problems involved in equating effective dose levels per injection across drugs.

METHODS

Subjects were 5 adolescent male rhesus monkeys (Macaca mulatta) weighing 5.5 to 8.2 kg. Four monkeys had a long history of morphine self-administration. Two were drug free and one had been maintained on cocaine (100 mcg/kg/inj) prior to buprenorphine self-administration. Monkey A319 had no previous drug self-administration history.

Monkeys worked at an operant task for food (1 gm banana pellet) and drug injections and were maintained at ad lib weight throughout the study. After training on a food administration task, each monkey was surgically implanted with a chronic double lumen catheter to permit intravenous drug self-administration. Details of the surgical procedures and operant apparatus have been published previously (Mello & Mendelson 1978).

Four periods of food availability, drug availability and time outs occurred each day. A one-hour food session was followed by a 1-hour drug session and 2 hours of time out (when responses had no programmed consequences). Experiments continued 24 hours a day, 7 days a week. The conditions of food and drug availability and time out periods each were associated with a different color stimulus light (S+) projected on a translucent response key on an operant panel. When saline was substituted for buprenorphine in control studies, saline was also associated with a distinctive colored stimulus light. Food and drug self-administration were maintained under a second order schedule of reinforcement {FR 3 (VR 16: S)}. An average of 16 responses on a variable ratio schedule (VR 16) produced a brief stimulus light (S+) of the appropriate color. However, a drug injection or a food pellet was delivered only after a fixed ratio of 3 (FR 3) of the VR 16 response requirements had been completed. Consequently, each food pellet or drug injection required an average of 48 responses. Second order schedules were used to minimize the possible disruptive effects of drug infusions on operant responding.

Each of 5 buprenorphine doses (.005, .01, .03, .05, .10 mg/kg/inj) was available for 60 consecutive drug sessions over 15 days. Buprenorphine doses were presented in an ascending order. However, the entire dose range was not completed by all monkeys. Buprenorphine hydrochloride solutions were diluted to the appropriate concentration for individual monkeys and doses are expressed in terms of salts. The upper limit of this dose range was determined in part by the solubility characteristics of buprenorphine.

The drug naive monkey and the drug free monkeys with a morphine self-administration history were given access to buprenorphine upon recovery from surgical implantation of an intravenous catheter. Buprenorphine was immediately substituted for cocaine without an intervening saline period. Each monkey began to work for buprenorphine on the same second order schedule of reinforcement previously required for food and cocaine self-administration.

After completion of the buprenorphine dose series, saline was substituted for buprenorphine, and monkeys were observed for signs of opiate withdrawal. Saline and food self-administration patterns were studied over 15 or more days.

RESULTS AND DISCUSSION

All monkeys self-administered buprenorphine over the range of doses studied irrespective of their previous drug history. Increases in the dose of buprenorphine per injection resulted in dose-related increases in the total amount of buprenorphine self-administered that day. Abrupt discontinuation of buprenorphine infusions did not result in discernible withdrawal signs. Monkeys consistently self-administered significantly more buprenorphine than saline. The effects of buprenorphine on food self-administration were inconsistent, but there were no significant changes in body weight as a function of chronic buprenorphine self-administration.

FIGURE 1

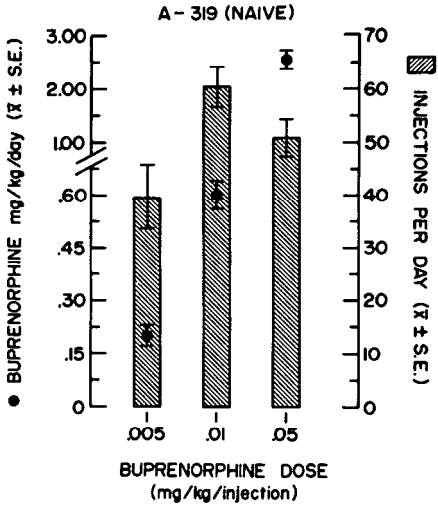


Figure 1 shows buprenorphine self-administration (mg/kg) and injections per day over 3 doses of buprenorphine (.005, .01, .05 mg/kg /inj) by a drug naive monkey. Each data point is the mean (± S.E.) of 60 drug sessions over 15 consecutive days. There was a significant increase ($p < .001$) in the daily dose of buprenorphine at each increase in the buprenorphine dose per injection. The number of injections per day also increased as the dose per injection increased. Injections per day of .01 mg/kg/inj were significantly higher ($p < .005$) than injections per day at a dose of .005 mg/kg /inj. Despite a tenfold increase in the dose per injection, the

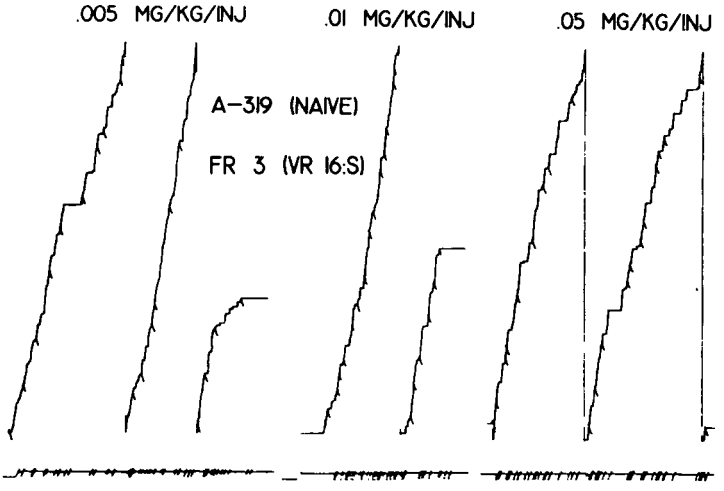
number of injections at .05 mg/kg/inj was greater than at .005 mg/kg/inj of buprenorphine.

Since the analgesic potency of buprenorphine is estimated to be between 25 and 40 times more than that of morphine, .20 mg/kg/day of buprenorphine is roughly equivalent to between 5 and 8 mg/kg of morphine; .60 mg/kg/day of buprenorphine is equivalent to between 15 and 24 mg/kg of morphine; and 2.55 mg/kg/day of buprenorphine is equivalent to between 63 and 102 mg/kg of morphine (cf. Figure 1).

Cumulative records of responding for buprenorphine on a FR 3 (VR 16:S) sechdule of reinforcement by the drug naive monkey are shown in Figure 2. A high steady rate of responding, (between 2 and 2.5 responses per second) was maintained across a tenfold increase in the buprenorphine dose per injection. Even at very high doses of buprenorphine, there was no evidence of sedation. As cumulative records at doses of .05 mg/kg/inj indicate, self-administration of 1 mg/kg of buprenorphine, the equivalent of 25 to 40 mg of morphine, did not suppress response rates.

Since this monkey was drug naive, his performance cannot be attributed to generalization from previous drug self-administration experience. He learned to self-administer buprenorphine very rapidly. He took 29 buprenorphine injections on the first day of exposure to a low dose of buprenorphine (.005 mg/kg/inj) and reached the final second order schedule requirement within 8 sessions on the first 2 days of buprenorphine exposure. In our experience, acquisition of morphine self-administration by naive monkeys on a VR 32 schedule of reinforcement required 3 to 4 weeks

FIGURE 2



and codeine acquisition by naive monkeys on a FR 30 schedule of reinforcement required almost 3 weeks (Woods 1977). The rapid acquisition of buprenorphine self-administration on a second order schedule is consistent with the interpretation that this drug is highly reinforcing in monkey.

Drug experienced monkeys also showed progressive increases in buprenorphine self-administration as the dose of buprenorphine per injection was increased. Data for 4 drug experienced monkeys are shown in Table 1. Three monkeys each took significantly more buprenorphine at doses of .03, .05 and .10 mg/kg/inj than at a low dose of .01 mg/kg/inj. Monkey A105 averaged a maximum of 2.95 mg/kg/day of buprenorphine at the highest dose level which is approximately equivalent to 72 to 166 mg/kg/day of morphine. In comparison to the lowest dose studied, injections per day remained stable, or increased significantly ($p < .05$, .01) as the dose per injection increased. One monkey (B205) did not show significant changes in buprenorphine self-administration across the range of doses studied. He took about .158 mg/kg/day,which is approximately equivalent to 3.9 to 6.3 mg/kg/day of morphine.

Table 1

BUPRENORPHINE SELF-ADMINISTRATION (mg/kg) OVER 60 SESSIONS ($\bar{X}$ ± S.E.)

MONKEY	BUPRENORPHINE DOSE PER INJECTION (mg/kg)				
	.005	.01	.03	.05	.10
DRUG NAIVE					
A-319	.20 (±.03)	.60* (±.04)	———	2.55*† (±.17)	———
MORPHINE HISTORY					
1-187	.16 (±.02)	.16 (±.04)	.72* (±.13)	———	———
B-205	.13 (±.03)	.17 (±.02)	.14 (±.05)	.24 (±.09)	.11 ±.04)
A-105	———	.19 (±.02)	.57** (±.07)	1.44**† (±.13)	2.95**† (±.24)
B-255	———	.09 (±.01)	.43** (±.03)	.62** (±.06)	.94**† (±.09)

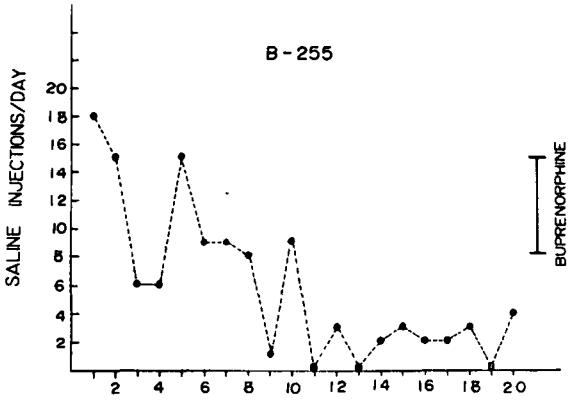
* Different from intake at .005 mg/kg/injection ($p < .001$)
** Different from intake at .01 mg/kg/injection ($p < .001$)
† Different from immediately preceeding value ($p < .01$ - .001)

Figure 3 shows illustrative data for the substitution of saline for buprenorphine for one monkey (B255) that took moderate buprenorphine doses. The range of the average number of buprenorphine injections taken across the dose range studied is shown at the right. This is a somewhat typical saline extinction curve insofar as high rates of saline maintained responding occurred during the first 10 days followed by a gradual decrease in saline injections. The number of saline injections taken during the first 10 days of saline substitution was significantly greater than during the

last 10 days ($p < .001$). Buprenorphine at all doses per injection maintained self-administration behavior significantly above the last 10 days of saline ($p < .001$).

FIGURE 3

SALINE SUBSTITUTION FOR BUPRENORPHINE



No discernible withdrawal signs or weight loss were observed in any monkey following prolonged buprenorphine self-administration. Withdrawal ratings were completed 3 times each day for 30 days in saline substitution trials and when a catheter became occluded. An absence of withdrawal signs after antagonist challenge in buprenorphine-maintained monkeys has been consistently reported (Cowan et al. 1977).

CONCLUSIONS

Buprenorphine is a positive reinforcer in rhesus monkey and maintains behavior leading to its administration on second order schedules of reinforcement, It appears comparable to morphine in reinforcing efficacy. These data are consistent with clinical studies of reactions to buprenorphine by heroin addicts (Jasinski et al. 1978). Addicts' reports of "liking" buprenorphine and its reinforcing properties in monkey, suggest that buprenorphine, like morphine, may have some abuse potential in man.

The abuse potential of any drug must be balanced against its safety and efficacy relative to other available compounds. In contrast to morphine or methadone, buprenorphine has been shown to produce minimal physical dependence in man. Its antagonistic properties virtually preclude overdose. Buprenorphine maintenance effectively reduces heroin self-administration by heroin addicts (Mello & Mendelson 1980) and it appears to offer some advantages as an analgesic (Houde 1979). Moreover, buprenorphine's agonistic properties could be advantageous if it were used as a pharmacotherapy for heroin addiction and as an analgesic for patients suffering from chronic pain.

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ACKNOWLEDGMENTS

These studies were supported in part by a grant from the Committee on Problems of Drug Dependence; the Biomedical Research Support Grant (5507 RR0584-16) to the McLean Hospital; and a grant from the National Institute on Drug Abuse (1 R01 DA02519-01). We thank Dr. Prabhat Sehgal for veterinary consultation.

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Correlations Among Certain Behavioral, Physiological, and Biochemical Effects of Narcotic Agonists

J. H. Woods, J. L. Katz, A. M. Young, F. Medzihradsky, and C. B. Smith

INTRODUCTION

Types of narcotic agonists nay be differentiated behaviorally according to their actions in various preparations. Morphine-liKe drugs ("mu" agonists) produce analgesia in rodents (Tyers, 1980) and are capable of suppressing completely the signs of deprivation-induced abstinence in morphine dependent rhesus monkeys (e.g., Deneau and Seevers, 1963). Additionally, these compounds share common interoceptive stimuli; rhesus monkeys trained to discriminate codeine or etorpnine from saline make drug-appropriate responses to other morphine-liKe drugs out not to behaviorally active drugs from other pharmacological classes (Woods et al., 1979a; Herling and Woods, in press). Moreover, a wide variety of morphine-like drugs maintain drug-reinforced responding in rhesus monkeys (Woods, 1977; Woods et al., in press; Young and Woods, in press).

Similar to mu agonists, ethylketazocine-like drugs ("kappa" agonists) produce analgesia in rodents (Tyers, 1980; Woods et al., 1978); however, these agonists fail to either precipitate or suppress abstinence in morphine-dependent rhesus monkeys (Woods et al., 1978; 1979b). These drugs also snare common intero-ceptive stimuli that are distinct from those of "mu" agonists; rhesus monkeys trained to discriminate ethylKetazocine from saline make drug-appropriate responses to ethylketazocine-like drugs out not to other behaviorally active drugs including mu agonists (Hein et al., in press; Woods et al., 1979a). In rhesus monkeys trained to self-administer codeine, kappa agonists (i.e., those that share ethylKetazocine's discriminative and direct effects) fail to maintain drug-reinforced responding (Woods et al., 1978; 1979a).

Thus, these types of narcotic agonists may be differentiated from each other on the basis of their actions in morphine-dependent monkeys, in monkeys trained to discriminate these agonists from saline, and in maintaining drug-reinforced responding. Mu and Kappa agonists also have characteristic actions upon two smooth muscle preparations, the isolated guinea-pig ileum and the mouse vas deferens (e.g., Kosterlitz and Waterfield, 1975). In both preparations, these agonists inhibit the electrically-induced twitch, and their effects are reversed by narcotic antagonists. Similarly, both types of narcotic agonists displace radiolabelled narcotics from binding sites in brain (Hutchinson, et al., 1975).

A number of investigators have noted the similarity of potencies across these preparations (Creese and Snyder, 1975; Hutchinson et al., 1975; Kosterlitz and Waterfield, 1975; Lord et al., 1978). The present study extends further the comparison of effects of narcotic agonists across a wider range of mu agonists and among some additional preparations. We nave compared across preparations a group of Kappa agonists that have been well identified and characterized behaviorally, allowing the evaluation of certain empirical generalizations about these classes of narcotic agonists and the identification of compounds that deviate significantly from the common spectra of action.

MATERIALS AND METHODS

Mouse vas deferens, Male, albino Swiss-Webster mice, weighing between 25 and 30 g, were sacrificed by decapitation. The vasa deferentia were removed, and 1.5 cm segments were suspended in organ baths which contained a modified Krebs' physiological buffer. The buffer contained the following: NaCl, 118mM; KCl, 4.75 mM; $CaCl_2$, 2.54 mM; $MgSO_4$, 1.19 mM; KH_2PO_4, 1.19 mM; glucose, 11 mM; $NaHCO_3$, 25 mM; hexamethonium bromide, 0.07 mM; pargyline, 0.3 mM; tyrosine, 0.2 mM; ascorbic acid, 0.1 mM; and disodium edetate, 0.03 mM. The buffer was saturated with 95% O_2-5% CO_2 and Kept at 37°C. The segments were attached to a strain gauge transaucer and suspended between two platinum electrodes. After a 15-minute equilibration period, the segments were stimulated once every ten seconds with pairs of pulses of 1 msec duration, 1 msec apart, and at supramaximal voltage. The segments were stimulated for 30 min or until a stable twitch height was achieved. Cumulative concentration-response curves were determined for the various drugs by increasing the concentration of the drug my three-fold increments until a maximum response was obtained. EC 50 values were calculated by probit analysis.

Guinea-pig ileum, The isolated guinea-pig ileum was prepared as described by Paton (1957). Segments of ileum were suspended in a Kreos physiological buffer at 37°C, saturated with 95% O_2-5% CO_2. The composition of the buffer was the same as described for the vas deferens preparation except that it contained

pyrillamine maleate, 0.125 mM, and did not contain the pargyline, tyrosine, ascorbic acid, or disodium edetate. Tissues were equilibrated for 30-40 minutes with washes every 10 min. After the equilibration period, cumulative concentration-response relationships were determined for the various drugs. EC 50 values were calculated by probit analysis.

^{3}H-Etorphine binding to rat brain membranes Male Sprague-Dawley rats, weighing approximately 200 g, were decapitated and the brains were excised at 4°C. The brains were homogenized in 50 mM Tris HCl buffer, pH 7.4, and centrifuged for 15 min at 20,000 x g. The pellet obtained was resuspended in cold buffer (1:100) and either frozen or used for the binding assay. The assay mixture consisted of 400 ul of the membrane suspension, 50 ul of H_20 or 1.6 M NaCl, 50 ul of either dextrorphan, levorphanol, or the narcotic drug under investigation and 25 ul of [15,16(n)-3H]etorphine (specific activity, 31 Ci/mmole, Amersham). The final concentrations of NaCl, dextrorphan, levorphanol, and etorphine in the medium were 1.5 x 10^{-1} M, 6 x 10^{-7} M, 6 x 10^{-7}M and 3 x 10^{-9} M, respectively. Incubations were carried out for a period of 15 min at which time the labelled etorphine was added. After a further incubation for 30 min, the tubes were placed on ice and their contents were filtered through Whatman GF/C filters previously washed in H_20. The samples on the filter were washed with 3 x 4 ml of ice-cold 50 mM Tris HCl, pH 7.4. Subsequently, the filters were placed in counting vials with 1 ml absolute ethanol and 10 ml of a dioxane-xylene-naphthalene scintillation mixture, and the vials were counted in a liquid scintillation spectrometer. Tne binding of ^{3}H-etorphine in the presence of a given drug was related to the maximum stereospecific etorphine binding, obtained as the difference between binding in the presence of excess dextrorphan and levorphanol. The EC 50 values were obtained graphically from log-probit plots of the binding data. Each drug was investigated at 5 or more concentrations, run in duplicate. In order to determine the sodium response ratio, the receptor assay was carried out both in the absence and presence of 150 mM NaCl in the medium. The sodium response ratio for a given drug was expressed as the ratio of EC 50 values obtained under those two experimental conditions.

Morphine-dependent rhesus monkey, Groups of rhesus monkeys were trained to routinely receive morphine injections and were maintained on a regular schedule of injections (3 mg/kg q 6 hr) that produces physical dependence in this species (Seevers and Deneau, 1963). After at least three months stabilization on the above schedule, morphine injections were periodically withheld, which was followed by the development of withdrawal signs. Fourteen hours after the last morphine injection, when abstinence signs are approximately half of the maximal severity, new compounds were tested for their ability to relieve the abstinence signs. Generally, morphine-like agonists suppress the abstinence signs whereas narcotic antagonists exacerbate those signs. In contrast to the morphine-like agonists, drugs identified as Kappa

agonists neither suppress nor exacerbate abstinence signs. Rather, these compounds at suitable doses produce a unique constellation of signs of sedation (Woods et al., 1979b). For further details of the procedure, and details on the grading of the various signs, see Deneau and Seevers (1963) and Villarreal (1973).

Drug self-administration, Rhesus monkeys were surgically prepared with chronic indwelling venous catheters and fitted with stainless steel harnesses which were connected by a jointed hollow arm to the back of the experimental cubicles. The catheter passed out the back of the monkey through the arm and to an infusion pump. Mounted on the front panel of the cubicle were one green and two red stimulus lights and two response keys. Experimental conditions and data collection were arranged by a digital computer.

Experimental sessions were conducted twice per day, during which pressing the right-hand key in the presence of the right stimulus light intermittently produced intravenous infusions of codeine phosphate (0.32 mg/kg) according to a schedule of one injection per 30 responses . Following each injection was a 600-sec period during which responses were ineffective and all lights were out. Sessions ended after 130 min or 13 injections, whichever came first. Different doses of test compounds were substituted for codeine on every fourth session. For further details of the apparatus or procedure see Deneau et al., (1969) and Woods (1977, 1980).

Drugs. The following were used: meperidine hydrochloride (v), fentanyl citrate (b), levorphanol hydrochloride (c), morphine sulphate (d), sufentanil citrate (f), etorphine hydrochloride (a), d-propoxyphene hydrochloride (w), dl-propoxyphene hydrochloride (e), ethylketazocine methane sulfonate (p), ketazocine methane sulfonate (q), methadone hydrochloride, ketobemidone hydrochloride, heroin hydrochloride, azidomorphine hydrochloride, UM 909: 2-(2-methyl-3-furylmethyl)-2'-hydroxy-alpha-5,9-dimethyl-6,7-nenzomorphan methane sulfonate (r), UM 911: 2-(3-methylfurfuryl)-2'-hydroxy-alpha-5,9-dimethyl-6,7-benzomorphan methane sulfonate (s), UM 983: N-(alpha-pyridyl), n-(l-beta-phenylethyl-4-piperidyl) ethylcarbamate hydrocnloride, UM 1070: (±)-5,9-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan hydrochloride (1R/S,, 5R/S, 9R/S, 2"R/S) (t), UM 1072: (±)-5,9-alpha-dimethyl-2'-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphan hydrochloride (1R/S, 5R/S, 9R/S, 2"R/S) (u), UM 1112: 2-cyclopropylmethyl-10- m-hydroxy-phenyl-trans-decahydroisoquinoline, UM 1113: 2-cyclopropylmethyl-10- m-hydroxy-phenyl-6-methyl-trans-decahydroisoquinoline, UM 1124: 1 m-[2-(cyclopropylmethyl)-1,2,3,4,4a,5,6,7,8,8a-decanydro-4a-isoquinolyl] phenol succinic acid salt, UM 1160: Structure not disclosed, UM 1167: (-)-17-cyclopropylmethyl-7,7-dimethyl-3-hydroxy-6,8-dioxamorphinan d-tartrate methanolate (g), UM 1169: Structure not disclosed (h), UM 1170: 4-beta-(m-methoxy-phenyl)-1,3-dimethyl-4 alpha-piperidinol proprionate hydrochloride

(x), UM 1173: dl-(1-(2- dimethylamino)ethyl)-6,7-dihydro-3-methyl-4-oxo-6-phenylindole-2-carboxylic acid ethyl ester (E) oxime, UM 1213: L-tyrosyl-D-alanylglycyl-L-N-alpha ethylphenyl-alanine amide acetate (k), UM 1220: N-(2-methoxyetnyl)-norketobemidone oxalate (l), UM 1233: N-(2-ethoxyethyl)-norketooemidone oxalate (n), UM 1238: Structure not disclosed (o). The letters following the drug names are used to designate compounds in Figure 1 and 2.

RESULTS AND DISCUSSION

Narcotic agonists which act upon mu receptors have been differentiated from those which act upon kappa receptors by comparing their relative potencies upon the isolated, electrically stimulated guinea-pig ileum and mouse vas deferens preparations (Hutchinson et al., 1975; Lord et al., 1978). Mu agonists were reported to be equipotent upon the two preparations, whereas kappa agonists were found to be more potent in suppressing the twitch of the ileum than in suppressing the twitch of the mouse vas deferens. The present study reevaluated the potencies of standard kappa agonists as well as certain mu agonists upon the two preparations and extends the number of mu agonists previously evaluated. Mu and Kappa agonists were identified by their behavioral actions as described above. The majority of the mu agonists were found to be roughly equipotent upon the two preparations (Table 1). Relative potencies upon the ileum when compared to the vas deferens ranged from one half as potent for UM 1167 and UM 1169 to slightly more than 4 times more potent for UM 1176. However, three mu agonists were much more potent upon the guinea-pig ileum than upon the mouse vas deferens, namely etorphine, fentanyl, and sufentanil. Sufentanil was remarkable in that it was found to be approximately 8 million times more potent upon the ileum than upon the vas deferens which suggests that this drug either interacts with a unique receptor in the ileum or that it possesses physical properties such as a very high degree of lipid solubility which increases its affinity for the mu receptor *in situ.* In contrast, UM 1170 is much more potent upon the mouse vas deferens than upon the guinea-pig ileum.

Kappa agonists also varied greatly in their relative potencies upon the two preparations. Ketazocine, UM 1070, and UM 1072 were approximately equipotent upon the two preparations. However, UM 909 and UM 911 were much less potent upon the ileum than upon the vas deferens. Only ethylketazocine was found to be more potent upon the ileum than upon the mouse vas deferens. Thus, tne present observations fail to support the contention that mu agonists are equipotent upon the two preparations whereas kappa agonists are more potent upon the ileum than upon the vas deferens. These observations suggest further either that narcotic agonists act upon a heterogeneous population of receptors in the two preparations or that individual drugs possess physical characteristics which alter markedly the manner in which they interact with one or more receptor type in each of the preparations.

TABLE 1

Potencies of "mu" and "kappa" agonists
on the mouse vas deferens and guinea-pig ileum

	Mouse vas deferens	Guinea-pig ileum	Ratio EC 50's
"Mu" Agonists	EC 50	EC 50	MVD/GPI
Sufentanil	4.43×10^{-9}	5.86×10^{-16}	8,000,000
Fentanyl	3.71×10^{-8}	1.34×10^{-10}	276.9
Etorphine	6.81×10^{-11}	4.76×10^{-13}	142.9
UM 1176	7.97×10^{-7}	1.86×10^{-7}	4.3
Meperidine	2.79×10^{-6}	9.75×10^{-7}	2.9
Morphine	1.83×10^{-8}	1.05×10^{-8}	1.7
UM 1238	7.28×10^{-8}	6.12×10^{-8}	1.2
UM 1177	6.22×10^{-7}	5.54×10^{-7}	1.1
UM 1213	1.09×10^{-8}	1.01×10^{-8}	1.1
UM 1220	3.19×10^{-7}	3.87×10^{-7}	0.8
UM 1167	8.68×10^{-10}	1.74×10^{-9}	0.5
UM 1169	8.38×10^{-7}	1.86×10^{-6}	0.5
UM 1170	7.78×10^{-8}	3.08×10^{-4}	0.0003
"Kappa" Agonists			
Ethyl-ketazocine	1.56×10^{-9}	1.49×10^{-10}	10.5
UM 1070	5.88×10^{-10}	6.50×10^{-10}	0.9
UM 1072	2.58×10^{-9}	3.30×10^{-9}	0.8
Ketazocine	1.18×10^{-9}	1.58×10^{-9}	0.7
UM 909	6.17×10^{-8}	1.90×10^{-6}	0.03
UM 911	1.21×10^{-8}	3.90×10^{-7}	0.03

The relationship between potencies of narcotic agonists upon the two physiological preparations and potencies in displacing ^{3}H-etorphine from opiate receptors on membranes isolated from rat cerebrum has been evaluated for mu and kappa agonists. Several investigators have compared the agonistic activity of opiates in the two preparations with displacement of various radiolabelled agonists and antagonists from rat brain membranes. Creese and Snyder (1975) found a high correlation between activity upon the guinea-pig ileum and activity in displacing ^{3}H-naloxone from rat brain membranes especially in the presence of sodium. Hutchinson et al. (1975) found a stronger relationship between displacement of ^{3}H-dihydromorphine from rat brain membranes and activity in the mouse vas deferens than between displacement and activity in the guinea-pig ileum. Finally, Kosterlitz and Leslie (1978) found a good correlation between displacement or ^{3}H-naloxone from rat brain membranes and from membranes isolated from the guinea-pig ileum and suggested that kappa agonists are less susceptible to the sodium effect than are mu agonists.

In the present studies a strong correlation was found between the EC 50's for the displacement of ^{3}H-etorphine from rat brain membranes and EC 50's upon the mouse vas deferens for the mu agonists. This correlation improved slightly when etorphine was excluded from the analysis. For displacement in the presence of sodium the correlation coefficient was 0.8559 and the slope of the regression line was 0.9879 which indicates equal potencies in the two preparations. In the absence of sodium the correlation coefficient was 0.9174 and the slope of the regression line was 0.8448. A relatively good correlation also exists between EC 50's for displacement and EC 50's upon the guinea-pig ileum if one excludes etorphine, fentanyl, and sufentanil from the analysis. In the absence of sodium, the correlation coefficient was 0.8838 and the slope was 0.8830. When etorphine, fentanyl, and sufentanil were added to the analysis, a lower correlation was found between potency on the ileum and displacement of ^{3}H-etorpine either in the presence or absence of sodium (Figure 1). Low correlations were also found between EC 50's for kappa agonists in either preparation and displacement of ^{3}H-etorphine from membranes isolated from rat cerebrum. It is possible that higher correlations will be found between the physiological effects of the various agonists and displacement of labelled ligands other than etorphine. The fact that etorphine is a mu agonist and that the correlations for mu agonists improve with the exclusion or etorphine supports this suggestion.

Correlations among effects of mu and kappa agonists upon mouse vas deferens or guinea-pig ileum and the 14-hr withdrawn monkey are shown in Figure 2. Drugs identified as kappa agonists do not suppress abstinence signs in the monkey; however, these compounds produce other overt effects including ataxia with marked body sag, dozing, and pronounced mydriasis. These effects can be antagonized by naloxone (Woods et al., 1978) indicating that, although they are different from those of morphine, they are narcotic effects.

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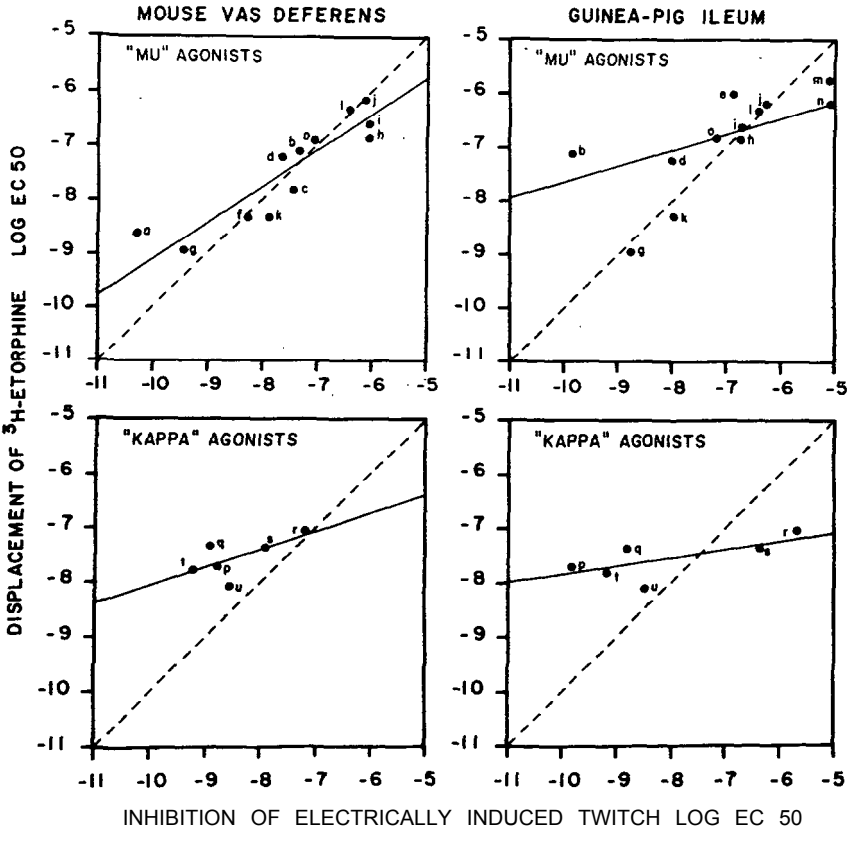
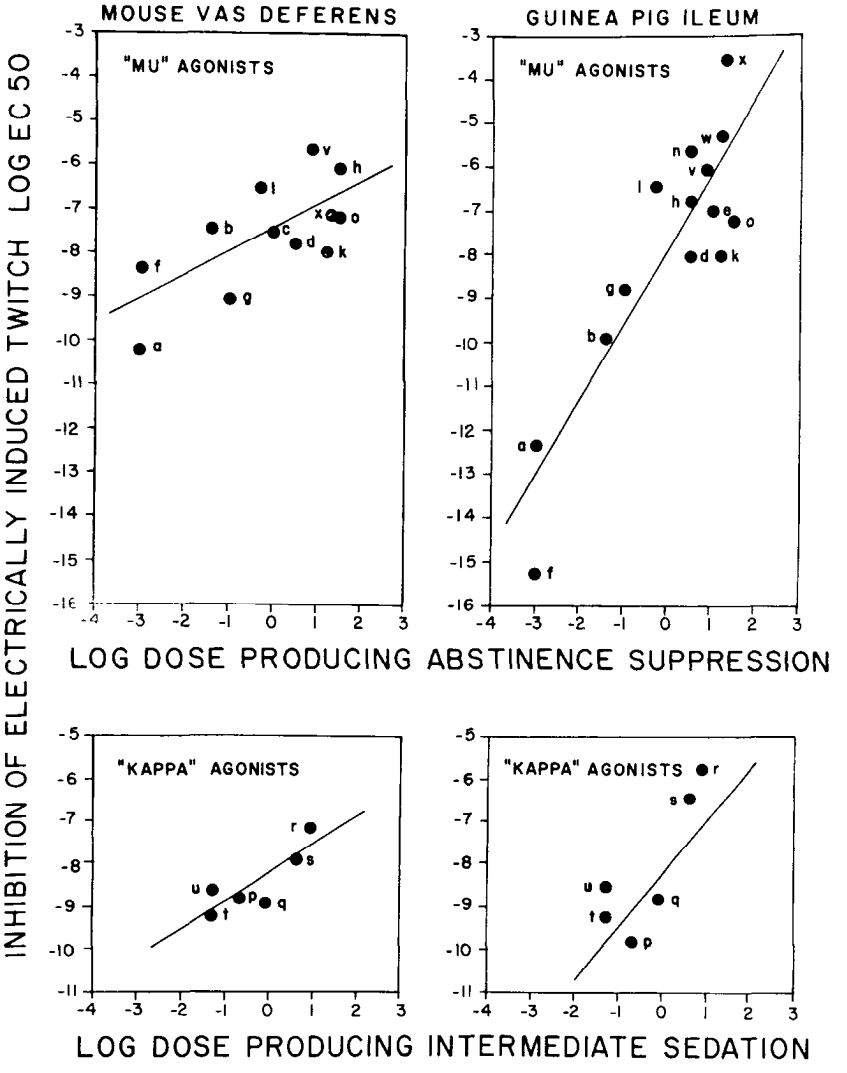
FIGURE 1



Correlations among effects of mu-type and kappa-type agonists upon tritiated etorphine bound to membranes from rat cerebrum. Abscissae: Log molar EC 50 for inhibition of electrically induced twitch of either mouse vas deferens (left panels or guinea-pig ileum (right panels). Ordinates: Log molar EC 50 for displacement of ^{3}H-etorphine from membranes of rat cerebrum. Upper panels: mu-type agonists; lower panels: kappa-type agonists. Lower case letters adjacent to points refer to drugs as coded in the Drugs section above. Solid straight lines were fitted to the points by the method of least squares. Broken lines indicate identical molar concentrations.

FIGURE 2



Correlations among effects of mu and kappa agonists upon smooth muscle preparations and 14-hr withdrawn rhesus monkeys. Abscissae: log dose, in mg/kg, that produced complete suppression of abstinence (upper panels) or log dose, in mg/kg, that produced an intermediate grade of sedation (lower panels). Ordinates: log EC 50 for inhibition of electrically induced twitch of the mouse vas deferens (left panels) or guinea-pig ileum (right panels). Lower case letters adjacent to points refer to drugs coded in the Drugs section. Straight lines were fitted to the points by the method of least squares linear regression.

Since the kappa agonists do not suppress abstinence, correlated here with effects on the physiological preparations are their sedative effects. Generally, correlations among the effects in smooth muscle with the in vivo effects were quite high for either guinea-pig ileum or mouse vas deferens. Most noticable were the differences in slopes of the regression lines that depended more on the particular physiological preparation than on the type of agonist or the type of behavioral effect observed. A similar relationship between slopes was obtained when effects on the two physiological preparations were correlated with analgesic effects obtained in mouse hot-plate tests (not shown). Thus, while relative potency in the mouse vas deferens underestimated relative potency in vivo. relative potency in the guinea-pig ileum overestimated relative potency in vivo.

Two mu-type agonists (d-, propoxyphene and UM 1233) snowed an unusual effect in the mouse vas deferens (Woods et al., this volume). These drugs suppressed abstinence signs in the 14-hr withdrawn monkey and inhibited the electrically driven guinea-pig ileum. In the mouse vas deferens, however, at suitable concentrations these drugs enhanced the magnitude of the twitch. Naltrexone further enhanced the increases in response magnitude produced by these compounds, suggesting a narcotic component to their actions that opposed the increased twitch. Indeed, at low concentrations, one of the drugs (UM 1233) produced a small inhibition of the twitch that was completely antagonized by naltrexone. Thus, while appearing to be morphine-like in the rhesus monkey, these compounds have other interesting, possibly noradrenergic, effects that obscure their narcotic actions in the mouse vas deferens.

The behavioral effects of the mu and kappa agonists obtained in the 14-hr withdrawn rhesus monkey were also correlated with the EC 50's obtained for the compounds in displacing tritiated etorphine bound to membrane preparations from rat cerebrum in the absence or sodium. While relatively better correlations were obtained with kappa-type than mu-type agonists (0.9417 vs. 0.7656, respectively), the slope for the regression line was relatively more steep for the mu-type agonists (mu: 0.65; kappa: 0.43). These differences in slope were not merely due to differences in the particular behavioral measures used for mu- and kappa-type drugs since they were consistent with the different slopes obtained when etorphine displacement EC 50's were correlated with analgesic ED 50's obtained in mouse hot-plate tests (not shown). Thus of the seven identified kappa-type agonists there was little difference in their potencies in displacing tritiated etorphine. In contrast, of the fifteen mu-type agonists studied there was a relatively wider range of potencies in displacing tritiated etorphine that approximated the range of potencies obtained in vivo.

Two compounds that were effective in suppressing abstinence signs in the 14-hr withdrawn rhesus monkey (meperidine and a meperidine analogue, UM 1170) were ineffective in displacing tritiated

etorphine in concentrations up to 2 x 10^{-6}M (Medzihradsky, unpublished data; Swain et al., 1979). Both of these compounds were also effective inhibitors of the electrically driven guinea-pig ileum and mouse vas deferens (see above). A third compound (UM 1213), while displacing etorphine with a relatively high potency, suppressed abstinence in the monkey with a relatively low potency. This compound is a synthetic peptide with opiate-like effects (Woods et al., this volume). Its low in vivo potency is probably a result of the high degree of degradation of the compound before it reaches its site of action.

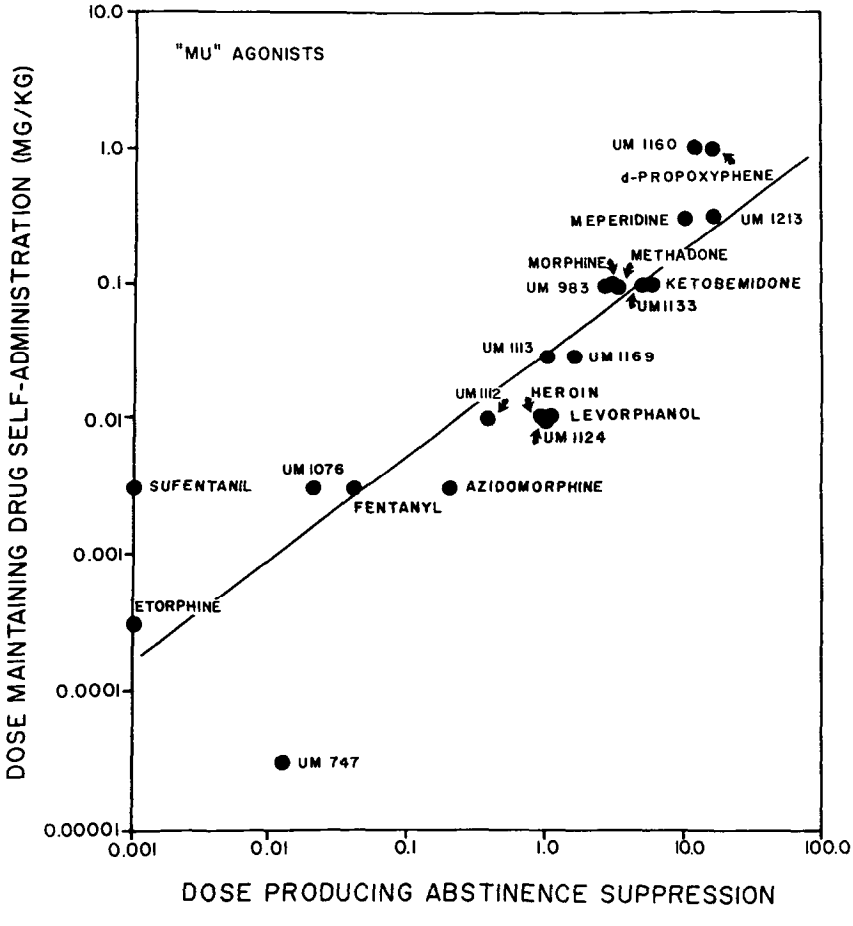
The potencies of mu agonists in suppressing abstinence in the 14-hr withdrawn rhesus monkey were also correlated with their potencies in maintaining drug-reinforced responding (Figure 3). The correlation between the mu agonists in exerting these in vivo effects in the rhesus monkey was 0.8704; the slope of the regression line was 0.77, suggesting a relatively good agreement between the relative potencies of the mu agonists in exerting these effects. Two interesting exceptions to this high correlation were noted. First, the regression line did not fit the points for very potent compounds such as etorpnine and sufentanil as well as it did points for less potent compounds. This disparity in the relative potencies of these compounds was also found in the comparisons of the effects of etorphine and sufentanil across the in vitro smooth muscle and binding preparations. Second, two compounds, UM 1167 and UM 1170, that were effective in suppressing abstinence in the 14-hr withdrawn monkey did not maintain drug-reinforced responding by the monkey (Swain et al., 1979; Woods et al., this volume). Interestingly, UM 1170 did not displace tritiated etorphine at concentrations up to 2 x 10^{-6} M.

SUMMARY

Relative potencies of Kappa and mu agonists on guinea-pig ileum compared to mouse vas deferens varied across a considerable range. In contrast to earlier reports (e.g. Hutchinson et al., 1975; Lord et al., 1978), the present differences in potency failed to distinguish between kappa and mu agonists, suggesting that distinctions between agonist types on the basis of their relative effects in these two preparations are unlikely to be generalizable. It remains possible that differences between this and previous studies may be due to differences in strain of subject, to minor differences in procedure, or to differences in the particular compounds studied. The study of a wider range of both mu and kappa agonists will provide further information on whether mu and Kappa agonists can be distinguished according to relative effects in these two preparations. Identification of additional compounds possessing kappa-like activity will be very useful.

In contrast to the correlation among effects in vas deferens and ileum, correlations among effects in either of these preparations with displacement of bound etorphine did distinguish between mu and kappa agonists. Slopes of regression lines for mu agonists

FIGURE 3



Correlations among doses of mu-type agonists that maintained maximal rates of responding under a fixed-ratio schedule of drug injection and that completely suppressed abstinence in the 14-hr withdrawn rhesus monkey. Abscissae: dose, in mg/kg on a log scale, that produced complete suppression of morphine abstinence on the Seevers scale; Ordinates: dose, in mg/kg on a tog scale, that maintained maximal rates of responding under a fixed-ratio schedule of intravenous drug injection in rhesus monkeys conditioned to self-administer codeine. A straight line was fitted to the points by the method of least squares.

were generally steeper than slopes for kappa agonists. This distinction was particularly clear in correlations of etorphine displacement and effects in the mouse vas deferens. With exclusion of exceptional compounds, slopes of lines fitted to mu and Kappa agonists in the guinea-pig ileum were also distinctive.

Correlations among effects in vas deferens or ileum with effects in the 14-hr withdrawn rhesus monkey showed an interesting differentiation between smooth muscle preparations but not agonist types. While all correlations were generally nigh, the slopes of regression lines in comparisons of in vivo effects with effects in ileum were steeper than with effects in vas deferens, indicating that effects in ileum overestimate while effects in vas deferens underestimate in vivo potency.

The displacement of etorphine and in vivo effects were also highly correlated, with some interesting exceptions. Noteworthy were meperidine and the meperidine analogue UM 1170. These compounds suppress abstinence in the withdrawn monkey but do not displace etorphine, suggesting that the narcotic actions of these compounds are mediated by distinctive recognition sites.

An important property of mu agonists is that they suppress abstinence in the morphine-dependent monkey. These effects were very closely correlated with the reinforcing effects of those drugs. In contrast, Kappa agonists neither suppress morphine abstinence nor maintain self administration. To the extent that the reinforcing effects are critical to the abuse liability of a compound, the kappa agonists may be a significant step towards compounds that are more useful analgesics.

The effects of narcotics have been studied in a variety of experimental preparations and many of their effects are highly correlated. An interdisciplinary approach comparing various effects of narcotics offers an approach that naturally highlights common characteristics of compounds. Possibly more important, the approach also delineates distinct types of narcotic agonists and individual compounds with unusual spectra of activity.

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ACKNOWLEDGMENTS

This report from the Drug Abuse Basic Research Program was supported by USPHS Grant DA-00254. The technical assistance of F. Adams, P. Dahlstrom, J. Goodrich, L. Labadie, and K. Watson is ackowledged with appreciation.

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Comparative Studies of the Pharmacological Effects of the d-and l-Isomers of Codeine

T. T. Chau and L. S. Harris

Opiates are known for their stereospecificity. The l-isomers are for example active as analgesics whereas the d-congeners are devoid of analgesic properties. Based upon these properties, first Goldstein et al., 1971, then other investigators have demonstrated the stereospecific binding of opiates and attempted to correlate such binding with specific opiate effects.

In our studies, the analgesic, antitussive, cardiovascular and binding properties of l-codeine were compared with those of d-codeine. An attempt was also made to demonstrate that the suppression of the cough reflex was mediated through receptors different from "opioid receptors."

METHODS

1. Antinociceptive effects of d- and l-codeine

The analgesic effects of l-codeine phosphate and d-codeine HBr, $2H_20$ were assessed in the mouse tail-flick test as described by D'Amour and Smith (1941) and in the hot plate test as described by Eddy and Leimbach (1953). Each mouse served as its own control. The antinociception response was calculated as % MPE (percent maximum possible effectiveness).

$$\% \text{ MPE} = \frac{\text{Test - Control}}{\text{Cut off - Control}} \times 100$$

The cut off time was 10 sec. in the tail-flick test and 30 sec. in the hot plate test. The drugs were given either s.c. or p.o. After the time of peak effect had been established for the tail-flick, all observations were then made at that time (20 min. post injection). The Litchfield-Wilcoxon method gave the ED50 and the 95% confidence limits (Litchfield and Wilcoxon, 1949).

2. Effects on cough reflex, blood pressure and heart rate

Cats weighing 3 to 4 kg were anesthetized with sodium pentobarbital 35 mg/kg i.p. The cough reflex was initiated by manual stimulation of the pharynx or lower part of the trachea with a probe through a small slit made in the trachea. The respiration rate, normal amplitude and the amplitude produced by the cough reflex were measured by a pneumograph and recorded on a polygraph. The control cough amplitude was initiated several times prior to the i.v. injection of the drug into the femoral vein. A decrease of the cough amplitude upon drug administration at different time points was defined as percent inhibition of the cough reflex. Different doses of each isomer were given and 3 cats were used for each dose. The Litchfield-Wilcoxon method gave the ED_{50} expressed as base and the 95% confidence limits.

The blood pressure was monitored via the femoral artery and the EKG leads gave the heart rate.

In other studies naloxone was given prior to d- or l-codeine but after the control cough had been obtained.

3. Inhibition of the stereospecific binding of ^{3}H-dihydromorphine

Several concentrations of d- or l-codeine ranging from 10^{-10} M to 10^{-4} M were added to whole-mouse-brain homogenates and tested for their inhibitory effects on 2.2 x 10^{-9} M ^{3}H-dihydromorphine stereospecific binding. The experiments were carried out as described by Pert and Snyder (1973).

RESULTS AND DISCUSSION

1. Analgesic effects

The antinociceptive effects of l-codeine phosphate were summarized in Table I.

d-Codeine HBr, $2H_20$ did not show any significant analgesic effect up to 100 mg/kg s.c. or p.o. in the tail-flick test. Hyperexcitability was observed at low doses (10 mg/kg). Convulsions were caused at higher doses and 100 mg/kg was lethal to all mice. In the hot plate test, the mice were particularly sensitive to the heat stimulus. No analgesia was observed from 10 to 75 mg/kg s.c. or p.o., the latter dose being lethal to all mice tested. Hyperalgesia at low doses and convulsions at higher doses were obtained with d-codeine.

Thus, in the antinociceptive test procedures, l-codeine was active whereas d-codeine had no analgesic effect up to lethal doses.

TABLE I

Antinociceptive Effects of l-Codeine in Mice

Test Procedure	Route of Administration	ED50 mg/kg and 95% C.L.[a]
Tail-Flick[b]	s.c.	4.09 (2.01 - 8.34)
N = 6	p.o.	13.41 (6.91 - 26.0)
Hot Plate[b]	s.c.	20.66 (11.52 - 37.08)
N = 6	p.o.	20.47 (14.63 - 28.67)

[a] Expressed as codeine phosphate

[b] The mice were tested 20 min. after injections of l-codeine phosphate.

2. Effects on cough reflex

The antitussive effects of l-codeine were summarized in Table II.

TABLE II

Antitussive Properties of l-Codeine Phosphate in the Cat

Dose mg/kg, i.v.	% Inhibition the Cough Reflex	Time of Maximum Effect
.25	15	30 min.
.3	53	3 min.
.5	82	6 min.
1.0	93	3 min.

ED_{50} of l-codeine base = .27 mg/kg (.14 - .47 mg/kg)

a. N = 3 per dose

b. Cats anesthetized with pentobarbital 35 mg/kg, i.p.

c. Cough reflex initiated by stimulation of the pharynx with a blunt-tipped probe

d. Recovery within 30 min. at .25 and .3 mg/kg

e. Recovery within 1 or 2 hours at .5 and 1.0 mg/kg

None of the doses changed the respiration rate or the amplitude of the normal respiration.

When 1 mg/kg naloxone HCl was given 4 or 5 min prior to the ED_{84} dose of l-codeine base (0.54 mg/kg), the antitussive effect of l-codeine was still observed in 2 cats tested. The cough reflex was still inhibited by 88% and by 84% in the 2 cats. Naloxone by itself did not interfere with the cough.

The antitussive effects of d-codeine HBr, $2H_20$ were shown in Table III. In one cat, 3 mg/kg, and in another cat, 4 mg/kg of d-codeine HBr, $2H_20$ somewhat decreased the respiration which became irregular, rapid but shallow for 4-5 min during which time the cough reflex could be still initiated. As with l-codeine, the ED_{84} dose of d-codeine (2.5 mg/kg) was not antagonized by 1 mg/kg naloxone given 5 min before.

TABLE III

Antitussive Properties of d-Codeine HBr, 2H2O in the Cat

Dose mg/kg, i.v.	% Inhibition of the Cough Reflex	Time of Maximum Effects
1	4	3 min.
2	40	6 min.
3	60	6 min.
4	95	6 min.

ED_{50} of d-codeine base = 1.61 mg/kg (.98 - 2.65 mg/kg)

a. N = 3 per dose

b. Cats anesthetized with pentobarbital 35 mg/kg, i.p.

c. Cough reflex initiated by stimulation of the pharynx with a blunt-tipped probe

d. Recovery within 30 min. at 1, 2, 3 mg and within 90 min. at 4 mg.

Thus, in our experiments, l-codeine and d-codeine showed good antitussive effects by decreasing the amplitude of the cough in a dose related manner, l-codeine being six times more potent than d-codeine. Their effects appeared to be mediated through receptors which were not sensitive to naloxone, since naloxone failed to prevent the antitussive effects of the 2 isomers.

3. Cardiovascular effects

l-Codeine phosphate, at the highest dose tested (1 mg/kg) caused a transient decrease in the blood pressure (20% decrease) in 2 out of 3 cats tested. In general, however, no significant cardiovascular effect was observed with l-codeine in the cats.

The cardiovascular effects of d-codeine were more pronounced, due probably to the higher doses which were given to the cats, as shown in Table IV.

TABLE IV

Cardiovascular Effects of d-Codeine HBr, $2H_2O$ in the Cat

Dose mg/kg, i.v.	Mean B.P.	Heart Rate	Recovery Time (min.)
1.0	No Effect	No Effect	----
2.0[a]	30% Decrease	20% Decrease	30
3.0[a]	64% Decrease	20% Decrease	40
4.0[b]	65% Decrease	22% Decrease	45

a. Effect in one out of three cats

b. Effect in two out of three cats

Three cats per dose

The hypotensive effects of the ED_{84} of l or d-codeine were not prevented by 1 mg/kg of naloxone. The blood pressure was still decreased by 18% with 0.54 mg/kg l-codeine base and by 30% with 2.5 mg/kg d-codeine base.

4. Inhibition of the stereospecific binding of ^{3}H-dihydromorphine

The concentration of l-codeine which inhibited the SSB of 2.2 x 10^{-9} M ^{3}H-dihydromorphine by 50% (IC_{50}) was 1.6 x 10^{-5}M (1.2 x 10^{-5}- 2 x 10^{-5}M). The d-isomer was inactive in this test up to 10^{-4} M. Although high-concentrations of l-codeine were required to displace ^{3}H-dihydromorphine from its specific binding sites, the stereospecificity of the 2 optic isomers could be still observed here. Enzymatic conversion of l-codeine to a more active metabolite (Adler, 1963) may explain the discrepancies between its in vivo analgesic effects and its in vitro binding properties. d-Codeine did not show any antinociceptive effect in our studies and did not bind to specific opiate receptors as expected.

In summary we have shown the stereospecific properties of the d- and l-isomers of codeine with respect to their binding properties and analgesic effects, The antitussive effects of the 2 isomers did not appear to be mediated by the classical opiate receptors as demonstrated by the lack of naloxone antagonism.

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ACKNOWLEDGMENTS

This work was supported by Grant DA-00490 from the National Institute on Drug Abuse. The authors gratefully acknowledge the generous supply of d-codeine provided by Dr. Arnold Brossi and his colleagues at the National Institute of Arthritis, Metabolism, and Digestive Diseases. A preliminary report of this work was presented at the 1980 FASEB meeting and a more complete report is in press at the Journal of Pharmacology and Experimental Therapeutics.

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WHO's Response to International Drug Control Treaties

I. Khan

I should like to review briefly the activities undertaken by WHO since I last reported to you in Philadelphia June 1979:

1. SCHEDULING ACTIVITIES

WHO's recommendations to the Secretary-General of the UN regarding the control status of eight substances were reviewed by the 6th Special Session of the UN Commission on Narcotic Drugs in February 1980 in Vienna. Tilidine and Sufentanil were placed in schedule I of the 1961 Convention while Dextropropoxyphene was placed in schedule II of the same Convention.

The Commission agreed with the recommendations of WHO that Phencyclidine continue to be controlled under schedule II of the 1971 Convention as it is needed in veterinary practices.

It was also decided that three analogues of PCP (TEP, PHP or PCPY and PCE) be controlled under schedule I and Mecloqualone under schedule II of the 1971 Convention.

In September 1980, WHO plans to review the status of a group of 9 substances (anorectics). These are:

Phentermine
Chlorphentermine
Chlortermine
Benzphetamine
Mazindol
Fenfluramine
Amfepramone
Phenmetrazine
Phendimetrazine

Phenmetrazine and Amfepramone are already controlled under schedule II and IV respectively of the 1971 Convention.

2. TECHNICAL COOPERATION WITH DEVELOPING COUNTRIES IN THE IMPLEMENTATION OF THE INTERNATIONAL DRUG CONTROL TREATIES

2.1 In the past, WHO has collaborated with a number of industrialized countries where data was made available to take scheduling decisions to control narcotic drugs under the earlier treaties. The 1971 Convention deals with psychotropic substances which are widely used in large doses for a long period of time and for ill-defined symptoms and disease entities. Many of these substances have been available on the market before the 1971 Convention was enforced in August 1976 or even formulated. Thus, data on the therapeutic usefulness of these substances and on their producing public health and social problems and the extent is needed. WHO is concerned and wishes to promote the active participation of its Member States, in particular the developing countries, in its programme on the implementation of the international drug control treaties.

2.2 Information on the needs of developing countries have been obtained through two WHO travelling seminars in the USSP. on the "Safe Use of Psychotropic and Narcotic Substances," when participants from 35 countries were present as well as a large number of Soviet officials and international and non-governmental organizations.

In 1979, a WHO staff member visited four countries within its four regions (AFRO, SEARO, EURO and PAHO) for discussions with officials responsible for the implementation of the international drug control treaties, members of the health profession and scientific community as well as those responsible for the trade and industry of drugs with dependence liability. These four countries have already ratified the 1971 Convention. In connexion with these visits, three reports on the "National Response to the Convention on Psychotropic Substances, 1971," by Finland (MNH/79.25), Thailand (MNH/79.36) and Madagascar (MNH/79.42), are available and a report on Argentina is in preparation.

2.3 NEED FOR DEVELOPMENT OF GUIDELINES FOR THE IMPLEMENTATION OF THE INTERNATIONAL DRUG CONTROL TREATIES

WHO has already identified a number of activities which require the development of guidelines to be considered by Member States, where needed. Some of these are:

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1. Development of guidelines for carrying out research, registration and re-registration of psychotropic substances with dependence liability with special reference to drugs modifying driving.

2. Need to limit and/or reduce the number of psychotropic substances linked to a clear policy on the availability of defined psychotropic drugs for the control of major neuropsychiatric disorders.

3. Mechanisms involving members of the various health professions in decision making to schedule drugs and their subsequent prescription control.

4. Development of drug utilization and drug monitoring systems for early identification of harm produced by psychotropic drugs and to take remedial steps.

5. Development of WHO guidelines for exemption of preparations containing more than one controlled psychotropic substance from certain control measures under article 3 of the 1971 Convention. Since the 1971 Convention allows parties to use their discretion and grant exemption, a need has been felt for WHO guidelines to be considered by countries while granting exemptions.

The report of the Director-General of WHO, (EB65.21) proposing the development of these guidelines was discussed at the 65th Session of the Executive Board in January 1980, and endorsed in its Resolution EB65.R7. Similarly, while considering the above documents, the 6th Special Session of the UN Commission on Narcotic Drugs which met in Vienna in February 1980, also endorsed the development of guidelines. The 33rd World Health Assembly also endorsed this in a resolution WHA33/27 of 23 May 1980.

I have observed during the last four years that the CPDD is becoming more and more involved in the subject of drug abuse, going further away from laboratory investigations in the field.

I should, therefore, like to request the Committee to consider collaborating with WHO in the development of these guidelines, as deemed fit.

3. A WHO Expert Committee on the Implementation of the Convention on Psychotropic Substances, 1971, will be held in Geneva to review methodology for assessing public health and social problems associated with drug abuse. The report of this Committee will be of assistance in identifying the harm caused by psychotropic substances, vis-a-vis their therapeutic benefit.

The Government of Finland has offered support to WHO in developing guidelines to assess the public health problems associated with the use of psychotropic substances.

WHO is planning to hold a Workshop in Finland in June 1981 in which 12 experts from developing countries will be invited to participate together with other resource persons. I would welcome a contribution from the CPDD to this meeting by deputing an expert.

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Potent Analgetics Derived From 9-Nor-9β-Hydroxyhexahydrocannabinol

M. R. Johnson, T. H. Althuis, J. S. Bindra, C. A. Harbert, L. S. Melvin, and G. M. Milne

SUMMARY

Based on the report of morphine-like analgetic activity of 9-nor-9β-hydroxyhexahydrocannabinol (HHC), we undertook a study of structural modifications of the C-3 side chain of HHC to optimize the analgetic activity. We ultimately examined four distinct classes of side chains: (1) alkyl (la-lc), (2) arylalkyl (ld-lh), (3) alkoxy (li-lj) and (4) arylalkyloxy (lk-lo). Three of these derivatives (lb, 1f, 1*l*) possessed analgetic activity 10X morphine. These studies demonstrate that the C-3 side chain of HHC can be modified in a structure-dependent fashion to yield potent, nonopioid analgetics. In addition, the effect of the 1 methyl-4-phenylbutyloxy side chain is unique among the side chains examined.

INTRODUCTION

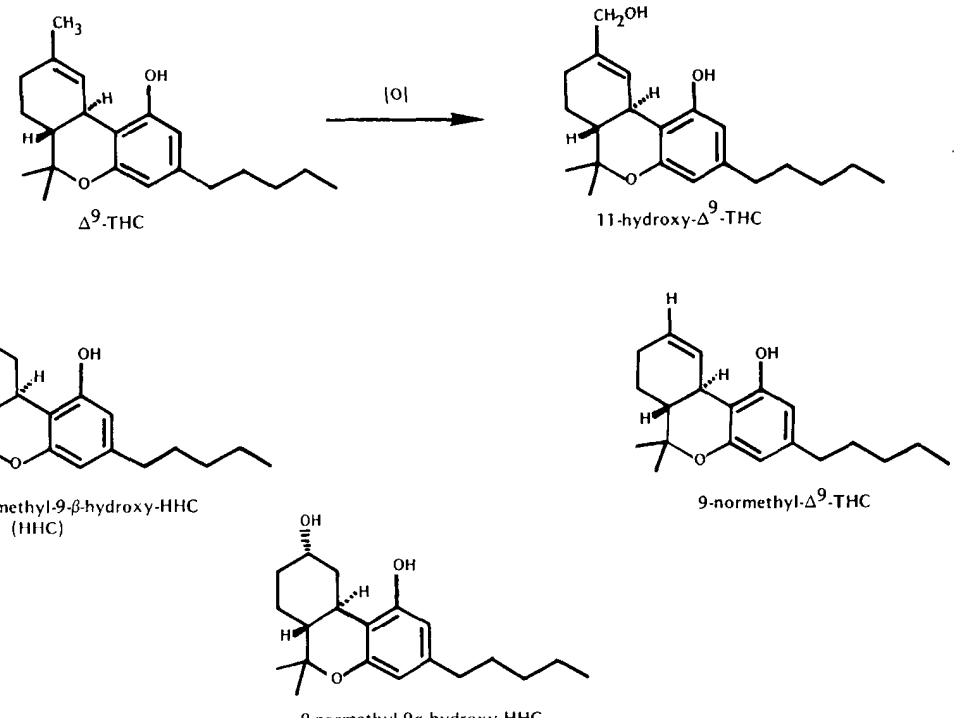
In 1974, May and Wilson postulated that the analgetic activity of Δ^{8}- and Δ^{9}-THC was due to their 11-hydroxy metabolites. They supported this conclusion by the observation that the 9-nor derivatives, which cannot be transformed into the 11-hydroxy metabolites, lack significant analgetic activity but exhibit dog ataxia and cardiovascular profiles nearly identical to Δ^{8}- and Δ^{9}-THC. During these studies (-)-9-nor-9β-hydroxyhexahydrocannabinol (HHC) was prepared and found to be analgetic with activity in the mouse hot plate test nearly equal to that of morphine. *We* report here on our study of structural modifications of the C-3 side chain of HHC; the objective was to determine if a further increase in analgetic activity was possible by structural alteration of the side chain.

METHODS

Subjects

Mice used in most of the studies were Charles River males, Swiss CD

PROTOTYPE CANNABINOID-RELATED STRUCTURES



Δ^9-THC

11-hydroxy-Δ^9-THC

9-normethyl-9-β-hydroxy-HHC
(HHC)

9-normethyl-Δ^9-THC

9-normethyl-9α-hydroxy-HHC

strain (17-21 g). Mice in the 2-phenyl-4-benzoquinone abdominal stretching experiment were Carworth males, albino CF-1 strain, weighing 11-15 g. Rats were Charles River males, Sprague-Dawley CD strain weighing 180-200 g unless otherwise noted.

Materials

Δ^9-Tetrahydrocannabinoid (Δ^9-THC) was supplied courtesy of Ms. Jacqueline R. Porter of NIDA. The side chain derivatives 1a-1o were synthesized by the Fahrenholtz (1967) procedure beginning with the appropriately substituted resorcinol. Pentazocine was graciously donated by Winthrop Laboratories. Morphine sulfate was purchased from Mallinckrodt Laboratories.

Routes of administration varied and are noted in the various individual studies. The compounds used in this study were dissolved and administered to rodents in a vehicle consisting of 5 percent ethanol, 5 percent Emulphor-620 and 90 percent saline. Solution concentrations were varied to allow a constant injection volume of 10 ml/kg of mouse and 5 ml/kg of rat.

Statistics

Data were calculated as the "% maximal possible effect," or % MPE as previously described (Milne et al. 1980)..

Tests of Analgesia

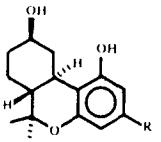
The tail-flick, tail-pinch, flinch jump and blockade of abdominal stretching after phenylbenzoquinone (PBQ test) tests were conducted according to previously published procedures (Milne et al. 1980). The method used for the mouse hot-plate test was modified after Woolfe and McDonald (1944).

RESULTS AND DISCUSSION

The finding of May and Wilson that analgetic activity was a dissociable feature of the cannabinoid molecule encouraged us to examine the effect of structural modifications at other positions of the cannabinoid molecule to more fully understand the optimum structural requirements for analgesia. One area that looked particularly attractive was the modification of the n-amyl C-3 side chain, since Adams and his co-workers (1949) demonstrated quite early that structural alterations of the C-3 side chain of synthetic Δ6a,10a-tetrahydrocannabinols markedly altered biological potency (Mechoulam et al. 1976). However, since many of the biological effects measured in these early studies were non-analgetic, we set out to carefully determine specific structure-analgetic activity relationships. Our search led us ultimately to examine four distinct classes of side chains which are summarized in table I along with their analgetic activity: (1) alkyl (1a-1c), (2) arylalkyl (1d-1h), (3) alkoxy (1i-1j) and (4) arylalkyloxy (1k-1o).

Initially, we examined the effect of the alkyl derivatives 1b and 1c, side chains previously used in the $\Delta^6$6a,10a-, Δ^8-, Δ^9-THC

TABLE I. ANALGETIC DATA (PBQ TEST)



Compound	R	Analgetic MPE_{50} (mg/kg)[a]
(-) Δ^9-THC		9.1 (5.4-12.3)
1a	$-CH_2CH_2CH_2CH_2CH_3$	0.63 (0.26-0.97)
1b	$-CH(CH_3)-CH_2Ch_2CH_2CH_2CH_3$	0.08 (.06- .09)
1c	$-C(CH_3)_2-CH_2Ch_2CH_2CH_2CH_2CH_3$	0.06 (.04- .08)
1d	$-CH_2CH_2C_6H_5$	>10[b]
1e	$-CH(CH_3)-CH_2CH_2C_6H_5$	4.66 (3.06-6.41)
1f	$-CH(CH_3)-CH_2CH_2CH_2C_6H_5$	0.06 (0.03-0.12)
1g	$-CH(CH_3)-CH_2CH_2CH_2$-4-C_5H_5N	0.22 (0.09-0.54)
1h	$-CH(CH_3)-CH_2CH_2CH_2CH_2C_6H_5$	0.35 (0.1-0.56)
1i	-O-c-C_6H_{11}	<10[c]
1j	$-O-CH(CH_3)-CH_2CH_2CH_2CH_2CH_3$	0.17 (0.13-0.23)
1k	$-O-CH(CH_3)-CH_2CH_2C_6H_5$	0.23 (0.13-0.33)
1l	$-O-CH(CH_3)-CH_2CH_2CH_2C_6H_5$	0.07 (0.03-0.12)
1m	$-CH(CH_3)-CH_2CH_2OC_6H_5$	0.23 (0.1-0.41)
1n	$-CH(CH_3)-CH_2CH_2CH_2-O-C_6H_5$	0.38 (0.18-0.51)
1o	$-CH(CH_3)-CH_2-O-CH_2CH_2C_6H_5$	1.28 (0.54-1.85)

(a) 0.3 hr. post. dose, s.c.
(b) 27% protection at 10 mg/kg, s.c.
(c) 75% protection at 10 mg/kg, s.c.

(Mechoulam, 1973; Mechoulam et al. 1976; Loev et al. 1973), and in the nabilone (Stark and Archer 1975) and nabitan (Pars et al. 1976) series. The use of a side chain branched at the benzylic position, such as 1b and 1c, considerably increased biological activity relative to the n-amyl side chain presumably, in part, due to a lessening of metabolic inactivation through benzylic oxidation. Side chain c has the further advantage that it does not introduce the additional diastereoisomers present in b. As can be seen in table I, both 1b and 1c exhibited analgetic activity considerably greater than HHC and Δ^{9}-THC.

Having demonstrated that it was possible to considerably increase the analgetic potency of HHC, we next turned our attention to aralkyl substituted derivatives in order to determine the effect of a pendant phenyl ring on analgetic activity (previously studied in the nabitan series by Winn et al. 1976). The unbranched phenethyl side chain (1d), which has the approximate extended chain length as n-amyl, had weak analgetic activity. However, the branched three, four and five carbon homologs exhibited potent, structure dependent analgetic activity with a maximum response at four linear carbon atoms (1f). The heteroaromatic 4-pyridyl derivative 1g, while somewhat less potent than 1f, retained analgetic activity. Molecular models show that 1f and 1g have approximately the same extended side chain length as 1b and 1c.

Previous studies in the $\Delta^{6a,10a}$-THC series have shown that an oxygen atom directly attached to the phenolic ring has a seemingly variable effect on biological activity. Thus, while unbranched ether side chains were reported to decrease activity (Mechoulam 1973), branched ether side chains exhibited a small increase in activity relative to their carbon isomers (Loev et al. 1973). These early studies did not address the effect these side chains had on analgetic activity, however, and furthermore, simultaneous changes in the C-ring and side chain have been shown to produce non-predictable SAR (Loev et al. 1973). Therefore, we reinvestigated this parameter to specifically assess the effect of an oxygen atom on analgetic activity in the HHC series. While the cyclohexyl derivative 1i retained some analgetic activity, the 2-heptyloxy derivative 1j possesses potent (2-3x morphine) analgetic activity. This finding encouraged us to pursue further the effect of a heteroatom in the C-3 side chain.

Introduction of oxygen in the aralkyl derivative 1e yielded 1k which was 20 times more potent than 1e. Increasing the chain length by one carbon yielded 1l which was fully as potent as 1f and 1c. Since the extended chain length of 1l is greater than 1c and 1f, this finding indicated that the oxygen atom itself and not just chain length affected analgetic activity. Furthermore, when the oxygen atom is not directly attached to the phenolic ring of HHC, it generally behaves as a carbon unit. Thus, 1n and 1o more closely resemble 1h than 1l. However, 1m does resemble its isomer 1k rather than 1f

Since many classes of "false" positive analgetics are active in the writhing assay, we selected a potent member of each side chain class to more fully evaluate analgesia across a broad range of stringent assays. Table II summarizes our results with 1b, 1f, 1J, 1l and 1n

versus the opiate agonist morphine, the mixed agonist-antagonist pentazocine, aspirin, Δ^9-THC and HHC (la). As is evident from table II, unlike Δ^9-THC, aspirin and pentazocine, these new derivatives exhibit potent, efficacious analgesia across a broad battery of tests and most closely resemble the opiate agonists in this respect. Even the potent analgetic la loses considerable efficacy in these more stringent tests of intrinsic analgetic activity.

We have shown that the C-3 side chain of HHC can be modified in a structure-dependent fashion to yield derivatives that produce potent analgesia in animals, previously characteristic only of the opiate analgetic class. In addition, we have shown that the effect of the placement of an oxygen atom directly attached to the aromatic ring of HHC is unique.

TABLE II. COMPARATIVE DOSES PRODUCING 50 PERCENT OF THE MAXIMUN POSSIBLE ANALGETIC EFFECT

Compound	MPE_{50} (mg/kg, s.c.) at Time of Estimated Peak Activity (95% Copfidence Limits)				
	PBQ Writhing[a]	Tail Flick[b]	Hot Plate[b]	Rat Tail Pinch[c]	Flinch Jump[c]
Morphine[a]	0.9 (0.4-1.3)	5.72 (2.73-10.59)	4.23 (1.98-7.02)	4.77 (3.5-5.8)	10.3 (6.6-13.8)
(-)-Δ^9-THC	9.1 (5.4-12.3)	55 (32.4-218.2)	>100	~133	83 (47.8-1217.3)
Pentazocine[a]	7.4 (1.3-13)	>56	>56	>56	>56
Aspirin (p.o.)	123 (106-132)	>100	>100	>100	>100
1a	0.63 (0.26-0.97)	9.1 (5.1.20)	34.4 (15.6-173)	70.5 (49.7-149.8)	36.4 (33.3-40.0)
1b	0.06 (.06-.09)	3. 0 (2.2-3.9)	.32-.56	N.T.	0.39 (.31-.47)
1f	0.06 (0.03-0.12)	0.25 (18-.3?)	.55 (.32-1.7)	.49 (.13-.84)	0.47 (.31-.66)
1j	0.17 (0.13-0.23)	N.T.	.56-1.0	.65 (.39-.96)	N.T.
1l	0. 07 (0.04-0.12)	.33 (.16-.48)	.46 (.23-.83)	.38 (.20-.58)	.38 (.33-.45)
1n	0.38 (0.18-0.51)	0.8 (.007-4.1)	10	N.T.	(1.4-13.8)

(a) Values at 0.3 hr post dose
(b) Values at 1 hr post dose
(c) Values at 2 hr post dose

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Preclinical Pharmacology of Doxpicodin, a New Analgesic

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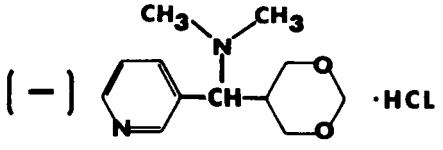
INTRODUCTION

Doxpicodin is a new analgesic which appears to exert its action through opiate-like receptors but is structurally different from other known analgesics. Doxpicodin is one member of a series of substituted 1,3-dioxanes whose synthesis and structure activity relationships have been previously reported (Booher et al. 1977). It produces an analgesic effect with a wide margin of safety in rodents and has demonstrated low physical dependence liability in monkeys. This paper reports the results of the preclinical studies on doxpicodin, a compound which is currently undergoing clinical evaluation.



DOXPICODIN

MATERIALS AND METHODS

Acetic Acid-Induced Mouse Writhing Analgesic Test. Fasted male Cox standard albino mice (Laboratory Supply Co., Mooresville, IN) weighing 20-22 gm were used. This method was similar to that previously described (Nickander et al. 1977).

Rat Tail Heat Analgesic Test. Fasted female Cox Sprague-Dawley rats (Laboratory Supply Co., Mooresville, IN) weighing 60-80 g were used in this test, which has been described earlier (Nickander et al. 1977; Robins, 1955).

Narcotic Antagonist Measures in Rats. The ability of the test compounds to reduce or antagonize the analgesic effect of morphine

was measured in the rat tail heat analgesic test (Zimmerman et al. 1977).

Affinity for Opiate Receptors of Rat Brain. Interaction of the compounds with opiate receptors of rat brain homogenates was measured by assaying the displacement of ^{3}H-naloxone and ^{3}H-dihydromorphine from specifically bound sites as described before (Wong and Horng, 1973). IC_{50}'s were determined as the oncentration at which a compound displaces 50 percent of bound ^{3}H-ligand.

Respiratory Depressant Measures in Conscious Rats. Experiments were conducted on male Sprague-Dawley rats weighing 300-325 g and fasted overnight. A carotid arterial cannula was permanently implanted by a method modified from Popovic and Popovic (1960). A cannula of PE60 medical grade tubing beveled bluntly from both sides was inserted into the carotid artery to a length of 22 to 25 mm. The exteriorized end of the cannula was plugged with a metal pin. A leather harness surrounded the chest and shoulders with openings for the forelegs, head, and trunk; and each animal was secured in a Stoelting holder.

On the day of test, 3 days after surgery, the rat was placed in an animal holder. After a 30-minute stabilization period a sample of 0.7 - 0.8 ml of blood was drawn anaerobically into a tuberculin syringe whose dead space had been filled with heparin. Blood gas values were determined within 10-15 minutes. The first blood sample was considered the "control" (pre-drug) and additional samples were drawn 30, 60, 120, 180 and 300 minutes after drug administration. The samples were analyzed on an Instrumentation Laboratory 513 pH/Blood Gas Analyzer that measured pH, pCO_2 and pO_2 directly.

Acute Toxicity and Its Antagonism by Naloxone in Mice. Mice were treated subcutaneously with either saline (10 ml/kg) or naloxone (10 mg/kg, s.c.) and a simultaneous dose of doxpicodin. There were 10-20 mice at each dose level. The number of mice dead at 7 hours was recorded. The LD_{50}'s and 95 percent confidence limits were calculated for both experiments according to the method of Litchfield and Wilcoxin (1949).

Mouse Withdrawal Jumping Procedure. Mice with free access to food and water were used. A chronic injection schedule was employed to induce physical dependence. The test compounds were administered subcutaneously at two different dose levels to look for a dose-response relationship. Injections were given at 8:00 a.m., 10:30 a.m., 1:00 p.m. and 3:30 p.m. The low-dose group received 32 mg/kg at each injection on the first and second days and 64 mg/kg on the third and fourth days. On the fifth day the mice received 32 mg/kg at 8:00 a.m. The high-dose group received double the amount of compound that the low-dose group received. The total doses achieved are indicated in RESULTS. Beginning one hour after the 8:00 a.m. treatment on the fifth day the mice were injected intraperitoneally with naloxone (100 mg/kg), immediately placed

individually into plexiglass cylinders, and the number of jumps was determined for 10 minutes.

RESULTS

Mouse Writhing Analgesic Test. Doxpicodin inhibited acetic acid-induced writhing in mice following both oral and subcutaneous administration. The ED_{50}'s compared to standard analgesics are shown in Table 1.

Doxpicodin's ED_{50} of 1.8 mg/kg s.c. was similar to that of meperidine and was 3 times that of morphine. Following oral administration, doxpicodin's activity was comparable to that of codeine and exhibited a p.o. to s.c. ratio of approximately 5 which was similar to that seen with codeine.

TABLE 1

ANALGESIC ACTIVITY OF DOXPICODIN IN THE MOUSE WRITHING TEST

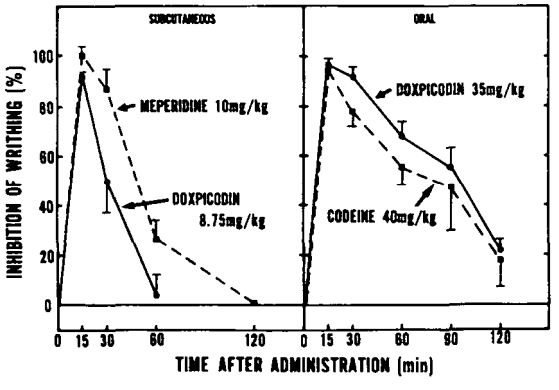
	*ED_{50}'s (95 PERCENT C.L.)	
COMPOUND OR TREATMENT	SUBCUTANEOUS	ORAL
DOXPICODIN	1.8 (1.2 - 2.7)	9.2 (6.8 - 12.6)
MORPHINE	0.64 (0.49 - 0.89)	3.9 (2.9 - 5.3)
CODEINE	2.3 (0.62 - 8.5)	12.6 (9.3 - 16.9)
MEPERIDINE	2.8 (2.3 - 3.10	16.4 (13.5 - 19.9)
PENTAZOCINE	2.0 (1.4 - 2.9)	46.0 (38.0 - 56.0)

*THE ED_{50} VALUE, DETERMINED AT THE PEAK TIME, IS THE DOSE (mg/kg) Required FOR A 50 PERCENT REDUCTION IN THE FREQUENCY OF WRITHINGS.

The duration of effects of doxpicodin (s.c. and p.o.) compared to meperidine (s.c.) and codeine (p.o.) are shown in Figure 1.

FIGURE 1

DURATION OF ACTION OF DOXPICODIN IN THE MOUSE WRITHING TEST



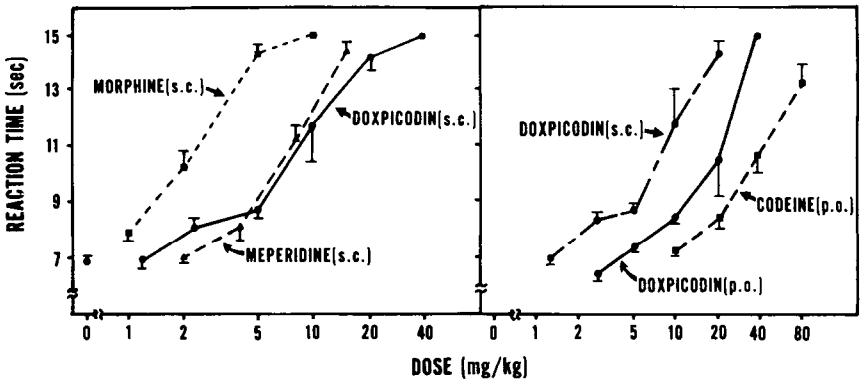
Following subcutaneous administration, doxpicodin and meperidine

showed rapid onsets of action and comparable short durations. The duration of action of doxpicodin was prolonged following oral administration while its potency was equivalent to that of codeine. The analgesic effects of doxpicodin in the mouse writhing test were blocked by the narcotic antagonist naloxone.

Rat Tail Heat Analgesic Test. Doxpicodin produced analgesia in rats as evidenced by prolongation of heat reaction times. Dose-response comparisons of doxpicodin, morphine, and meperidine following s.c. administration in the rat tail heat test are shown in Figure 2.

FIGURE 2

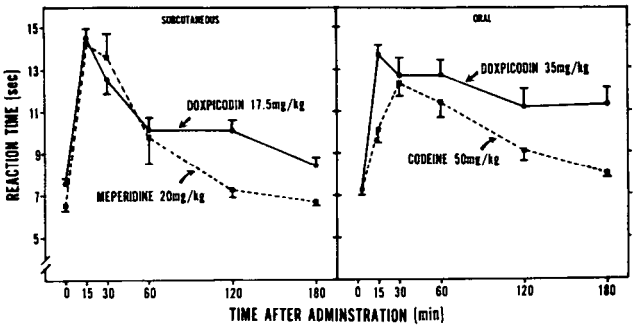
COMPARATIVE DOSE EFFECTS OF DOXPICODIN IN THE RAT TAIL HEAT TEST



Doxpicodin is equivalent in potency to meperidine and 1/3 as potent as morphine. Doxpicodin was nearly 1/2 as potent by the p.o. route compared to the subcutaneous route (Figure 2). The dose-effect of doxpicodin compared to codeine following p.o. administration is also shown in Figure 2. Doxpicodin appears to be significantly more active than codeine. The analgesic effects of doxpicodin in the rat rail heat test were also blocked by naloxone.

FIGURE 3

DURATION OF ACTION OF DOXPICODIN IN THE RAT TAIL HEAT TEST



The time effects of doxpicodin in the rat tail heat test are shown in Figure 3. Doxpicodin's peak effect by the s.c. route is similar to that of meperidine, however, doxpicodin appears to have a longer duration of action. Following p.o. administration a dose of 35 mg/kg of doxpicodin produced significantly greater analgesia than 50 mg/kg, p.o. of codeine and had a longer duration of action.

Narcotic Antagonist Measures in Rats. The ability of doxpicodin to reduce or antagonize the analgesic effect of morphine was examined in the rat tail heat analgesic test. Doxpicodin failed to reduce the analgesic action of morphine but did show additive effects.

Opiate Receptor Binding. Receptor affinities of doxpicodin, as measured by its inhibition of ^{3}H-naloxone and ^{3}H-dihydro-morphine binding to rat brain synaptic membranes, are shown in Table 2. Doxpicodin with an IC_{50} of 1.7×10^{-6}M is far less potent than morphine but comparable to meperidine in competing for ^{3}H-dihydromorphine binding sites. The displacement of 3H-naloxone by doxpicodin ($IC_{50} = 5 \times 10^{-6}$M) though weak is reduced approximately 5-fold in the presence of sodium.

TABLE 2

INHIBITION OF ^{3}H-NALOXONE AND ^{3}H-DIHYDROMORPHINE BINDING BY DOXPICODIN

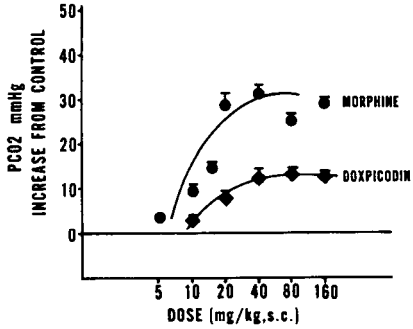
^{3}H-LIGAND	NaCl ADDED	IC_{50}* (M) DOXPICODIN	MORPHINE	MEPERIDINE
^{3}H-DIHYDROMORPHINE	-	1.7×10^{-6}	1.5×10^{-9}	2×10^{-6}
^{3}H-NALOXONE	-	5×10^{-6}	5.2×10^{-9}	
^{3}H-NALOXONE	+	23×10^{-6}	230×10^{-9}	

*CONCENTRATION OF COMPOUND AT 50 PERCENT INHIBITION.

Respiratory Depressant Measures in Conscious Rats. The respiratory depressant effects of doxpicodin as measured by arterial blood pCO_2, pO_2 and pH have been evaluated in conscious rats and compared to that of morphine. The subcutaneous dose-effect of morphine and doxpicodin on arterial blood pCO_2 are shown in Figure 4. The effects were compared 120 min after treatment, a time at which both compounds were near maximum effect. For both morphine and doxpicodin, there was an initial dose-related increase in pCO_2 followed by an apparent plateau with increasing dose. During the initial dose-related phase morphine was approximately 4 times as potent as doxpicodin. However, the maximum achievable depressant effect for morphine, as indicated by increases in pCO_2, was at least twice that observed with doxpicodin. In accord with these results, administration of morphine and doxpicodin produced dose-related decreases in pO_2 and pH. The maximum achievable decreases with morphine were again twice that of doxpicodin. The effects on blood pCO_2, pO_2 and pH by both morphine and doxpicodin were reversed by naloxone.

FIGURE 4

DOSE EFFECT OF DOXPICODIN AND MORPHINE ON ARTERIAL BLOOD PCO_2 IN RATS



Acute Toxicity Measures in Mice. The subcutaneous LD_{50} (95 percent Confidence Limits) of doxpicodin in mice was found to be 1420 (1297 - 1555) mg/kg. Simultaneous treatment with naloxone significantly reduced the acute toxicity of doxpicodin resulting in a LD50 value of 1840 (1688 - 2006) mg/kg. Using the ED_{50} from the mouse writhing assay, doxpicodin has a margin of safety greater than 750.

Physical Dependence Measures in Mice and Monkeys. The ability of doxpicodin to produce physical dependence following chronic subcutaneous administration in mice was estimated using the mouse withdrawal jumping test and compared to those of codeine and pentazocine. The results of this test are presented in Table 3. The maximum doses used for codeine and pentazocine were limited because of toxicity. The jumping activity due to doxpicodin was less than or equal to that of pentazocine and considerably less than that seen with codeine.

TABLE 3

EFFECT OF DOXPICODIN IN THE MOUSE WITHDRAWAL JUMPING TEST

COMPOUND	TOTAL DOSE MG/KG, s.c.	N	JUMPS/MOUSE (MEAN ± S.E.)	JUMPING(%) ≥1	JUMPING(%) ≥10
SALINE	-	30	3.5 ± 1.0	43	20
DOXPICODIN	800	15	5.1 ± 2.5	33	20
	1600	20	11.6 ± 4.1*	50	35
PENTAZOCINE	800	15	9.5 ± 2.9	64	47
	1088	15	13.6 ± 3.1*	67	60
CODEINE	800	15	25.3 ± 4.9*	100	80
	1280	17	36.9 ± 4.4*	100	94

*SIGNIFICANTLY GREATER THAN CONTROL ($P < 0.05$).

The physical dependence liability of doxpicodin in monkeys was assessed at the University of Michigan and the Medical College of Virginia under the auspices of the Committee on Problems of Drug Dependence. In the single dose suppression test doses as high as 75 mg/kg failed to alter the withdrawal syndrome (Swan et al. 1977; Aceto et al. 1977). In the test for primary physical dependence, doxpicodin administered every 6 hr at a maximum dose of 150

mg/kg s.c. No withdrawal signs were apparent either after abrupt withdrawal or when given a naloxone challenge (Aceto et al. 1977).

CONCLUSIONS

In rodents doxpicodin exhibits analgesic activity comparable to that seen with meperidine and codeine and appears to exert this effect by an action at the opiate receptor. Acute toxicity measures in rodents indicate a wide margin of safety, a result supported by the demonstration of limited respiratory depression in conscious rats. Doxpicodin's low physical dependence liability novel structure,and encouraging pharmacological profile suggest it may be a safe and useful analgesic in man.

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Pharmacologic Effects of N-Allylnormetazocine (SKF-10047)

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INTRODUCTION

N-allylnormetazocine (SKF-10047; Win-19,631) possesses potent psychotomimetic activity in man (Keats and Telford 1964) and also is an effective antagonist of meperidine analgesia in the rat having little or no detectable antinociceptive properties itself (Archer et al. 1964; Pearl and Harris 1966). In the chronic spinal dog, SKP-10047 caused mydriasis, tachypnea, tachycardia and mania, effects which were quite unlike those induced by morphine or ketocyclazocine; Martin and coworkers (1976) then proposed that the pharmacologic effects of SKF-10047 culminate from opiate action at a putative σ opioid receptor and not from μ (morphine) or κ (ketocyclazocine) opioid receptors.

The bizarre behavior -- consisting of mild ataxia, lateral head movements, pivoting of hindpaws and walking backwards (Schneider 1968; Buckett and Shaw 1975) and peculiar circular movements turning to one direction only (Ahtee and Kääariäiren 1973) -- induced by cyclazocine in the rat is purportedly caused by its σ activity, activity which is also shared by other opioids such as nalorphine, levallorphan and pentazocine in addition to SKP-10047. Recently, in novel environment, SKF-10047 and cyclazocine both caused circling, rearing and side-to-side head movements in addition to increasing the seizure threshold in rats (Cowan et al. 1979).

It was reported that SKF-10047 potently displaced radiolabelled phencyclidine bound specifically to a saturable class of binding sites in rat brain membrane preparations (Zukin and Zukin 1979), although the data have been contested (Maayani and Weinstein 1980). In any event, the finding is significant in that chronic abuse of phencyclidine in man resembles schizophrenia with symptoms including auditory hallucination, inappropriate affect, and agitation. Thus, the psychotomimetic activity induced by the putative a opioid agonists might arise from receptor activation of an appropriate "psychotomimetic" receptor. One possible common underlying mechanism of action in PCP-induced and SKP-10047-

induced hallucinations in man and the bizarre motor effects in rats and dogs may be an excess of central dopaminergic receptor activities. For example, it has been noted that acute amphetamine overdose resembles part of the acute schizophrenia syndrome. In addition, Martin has shown that some signs induced by SKF-10047 in the dog were mimicked by the dopaminergic agonist, apomorphine. The following study was designed to characterize some of the pharmacologic effects of N-allylnormetazocine in the rat with respect to central dopaminergic mediation.

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 250 to 450 g at the time of the experiments were housed in the testing room under automatically controlled conditions. Locomotor activity in the horizontal plane was recorded by an activity monitor equipped with two arrays (X,Y) of 15 infrared beams (Opto-Varimex-ATT, Columbus Instruments, OH) and assessed between 1100 and 1800 hours. Antinociception was measured by the hotplate method of Eddy and Leimbach (1953) as modified by O'Callaghan and Holtzman (1975); the surface temperature was maintained at 49.5 ± 0.1°C. The nociceptive endpoints were a licking of the hindfeet, jumping onto the cylinder rim or a lifting of one of the hindfeet for greater than 2 seconds. Test latencies no greater than 45 seconds were subtracted by the control response latency, an average of three predrug trials, to give "change in latency." The drugs used were: SKF-10047 and ketocyclazocine methanesulfonate (generous gifts from Sterling-Winthrop Research Institute, Rensselaer, NY); spiperone (gift from Janssen Pharmaceutics, Beerse, Belgium); clonidine hydrochloride (gift from Boehringer Ingelheim Ltd., Ridgefield, CO); apomorphine hydrochloride (Sigma); naltrexone hydrochloride (gift from Endo Laboratories, Inc., Garden City, NY).

6-Hydroxydopamine Lesions

Separate groups of animals were lesioned with 4 µg of 6-hydroxydopamine (6-OHDA) injected into the right substantia nigra as described previously (Iwamoto et al. 1976) and used in the circling behavior experiments after three weeks.

RESULTS

Locomotor Behavior

Locomotor activity was stimulated up to 120 minutes after 10 mg/kg of SKF-10047 (Fig. 1). Other behaviors observed after SKF-10047 were sniffing and alternating backward locomotion. A heroic dose of naltrexone, 20 mg/kg s.c., given at -15 minutes significantly decreased locomotor activity induced by 10 mg/kg s.c. of SKF-10047. Thirty minute pretreatment with 0.15 mg/kg s.c. of spiperone strongly inhibited SKF-10047-induced locomotion by over 94 percent; this dose of spiperone did not produce cataleptic behavior. Clonidine administration, 0.1 mg/kg s.c., diminished the SKF-10047-induced locomotor response by 67 percent

FIGURE 1

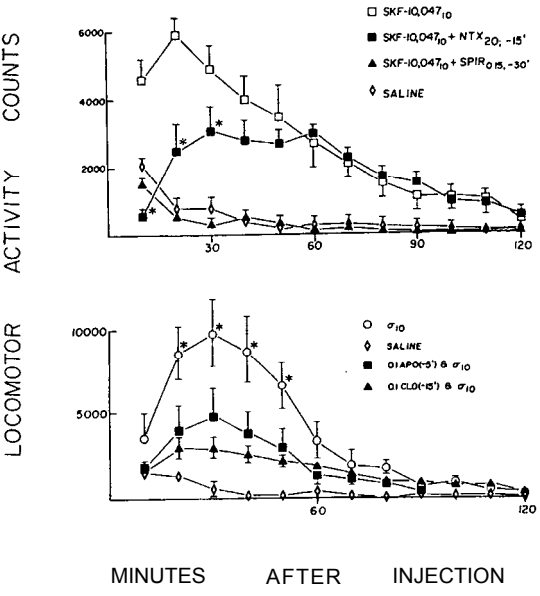
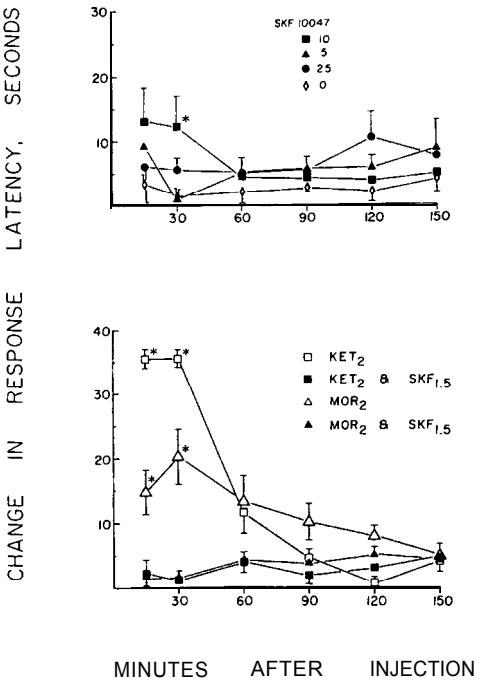


FIGURE 2



between 10 to 60 minutes after injection. Similarly, 0.1 mg/kg s.c. of apomorphine significantly reduced the SKF-10047-induced locomotor activity by 54 percent (Fig. 1).

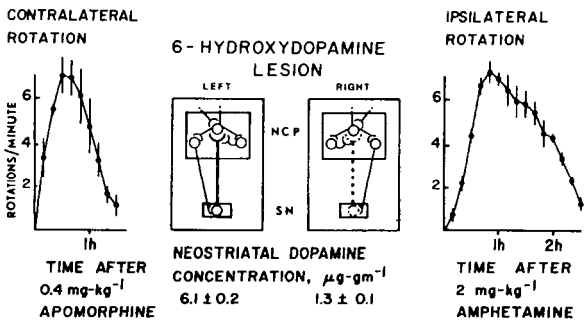
Antinociception

SKF-10047 did not produce analgesia as assessed by the 49.5°C hotplate in agreement with previous reports (Fig. 3). Also in keeping with past data, 2 mg/kg of either morphine or ketocyclazocine produced potent antinociception on the "warm" hotplate. Significantly, 1.5 mg/kg s.c. of SKF-10047 antagonized the analgesic effects of both morphine and ketocyclazocine (Fig. 2).

Circling Behavior

In the unilateral 6-OHDA-lesion - circling behavior model, in which ipsilateral intracaudate dopamine levels are diminished by almost 80 percent 28 days after lesioning, d-amphetamine-induced dopamine release in the intact striatum causes circling behavior towards, or ipsilateral to, the lesion. In contrast, direct stimulation of supersensitive dopamine receptors in the lesioned striatum after apomorphine injection causes contralateral circling behavior (Fig. 3).

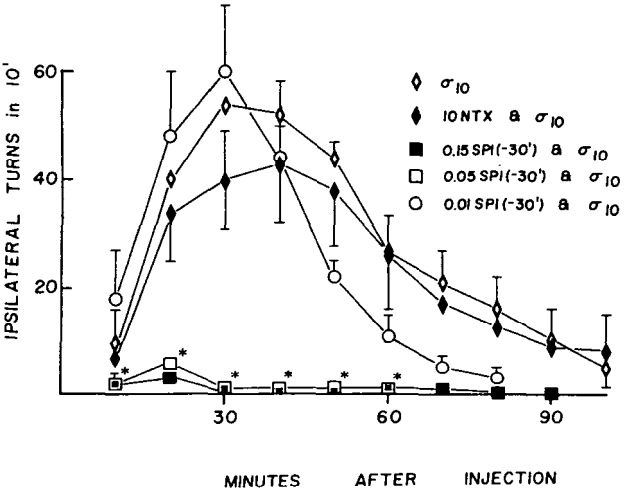
FIGURE 3



Using the circling model, SKF-10047 administration of 6-OHDA-lesioned rats caused high intensities of ipsilateral circling behavior that was not antagonized by 10 mg/kg naltrexone pretreatment (Fig. 4).

In similarity to the effects of SKF-10047 on spontaneous activity, the SKF-10047-induced circling behavior was antagonized by the putative dopamine receptor blocker, spiperone, at the 0.15 and 0.05 mg/kg doses, but not at 0.01 mg/kg s.c. (Fig. 4).

FIGURE 4



These results demonstrate clearly that SKF-10047 increases spontaneous locomotor activity and causes ipsilateral circling behavior, both of which are not easily antagonized by naltrexone, but which are significantly diminished by the dopamine receptor blocker, spiperone. The data from 6-OHDA circling behavior model suggests that SKF-10047 indirectly activates the intact dopaminergic mesostriatal pathway, perhaps by blocking reuptake of dopamine, by releasing dopamine as after amphetamine to cause the observed ipsilateral turning behavior, or by stimulating the mesostriatal path at the level of the cell bodies directly. The fact that a putative dopamine receptor blocker, spiperone, was able to antagonize the locomotor activity and circling behavior induced by SKF-10047, supports the hypotheses that SKF-10047 increases the activity within dopaminergic neurons. Thus, both SKF-10047 and morphine (Iwamoto et al. 1976) induce ipsilateral circling behavior, although the present data illustrate that the SKF-10047 compound is much more potent than morphine in this regard.

Stimulation of presynaptic dopamine receptors after 0.1 mg/kg of apomorphine causes an inhibition of nerve impulse flow within the pathway (Bunney et al. 1973). Thus, if locomotor activity induced by SKF-10047 depended upon neuronal transmission through dopaminergic pathways, it can be expected that inhibition of transmission after presynaptic dopamine receptor stimulation would diminish locomotion; this, in fact, was observed as presented in Figure 1. In addition, a role for noradrenaline cannot be excluded since clonidine also blocked SKF-10047-induced locomotor behavior. However, separate experiments not illustrated showed that brain levels of morphine 30 minutes

after 2 mg/kg s.c. morphine sulfate are decreased by 49 percent by 0.1 mg/kg clonidine; whether clonidine also diminished brain levels of SKF-10047 is not known at this time. Finally, the fact that SKF-10047 antagonized both morphine-induced and keto-cyclazocine-induced antinociception would suggest that SKF-10047, in addition to its known properties as a μ opioid receptor antagonist, also possesses antagonist actions at the putative κ opioid receptor.

In conclusion, the present data indicate that opioid-induced hypermotility may originate from a σ opioid receptor interaction and may also depend upon the integrity of central dopamine-containing systems since SKF-10047-induced locomotion can be disrupted by both presynaptic and postsynaptic inhibitors of dopamine transmission.

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Clonidine vs. Methadone for Opiate Detoxification: Double-Blind Outpatient Trials

A. M. Washton and R. B. Resnick

INTRODUCTION

Stemming from earlier demonstrations that a single dose of clonidine reduces signs and symptom of opiate withdrawal (Gold et al., 1978; Washton et al., 1980a) open clinical trials have shown that clonidine can be used safely and effectively for the clinical management of opiate detoxification in both inpatient (Gold et al., 1980) and outpatient (Washton et al., 1980a; 1980b) settings. For example, we reported that following abrupt temination of 5 to 40 mg chronic methadone, 31 of 43 patients or 72 percent were able to remain opiate free on clonidine for the 10 days necessary to initiate opiate antagonist treatment with naltrexone (Washton et al., 1980b). Our studies further indicated that to achieve safe and effective control of withdrawal symptom with clonidine on an outpatient basis, the clonidine dose regimen must be individualized and titrated according to each patient's symptoms and blood pressure because of varying sensitivity to clonidine's antiwithdrawal, sedative, and hypotensive effects.

These clinical studies indicated that clonidine might be a potentially valuable pharmacologic aid in addiction treatment, particularly since it is the only nonopiate medication shown to have specific and significant antiwithdrawal effects. It has been suggested that clonidine might even be superior to conventional methadone detoxification procedures (Gold et al., 1980) but thus far no controlled clinical investigations have been carried. out.

We have now conducted a randomized double-blind placebo-controlled study comparing clonidine and methadone detoxification procedures.

SUBJECTS AND METHOD

The subjects were 26 opiate-dependent outpatient volunteers who showed no evidence of serious medical or psychiatric illness and gave informed consent to participate in the study after receiving a full explanation of the experimental procedures. They ranged in

age from 22 to 49 years (mean 31 years) with addiction histories of 3 months to 25 years (man 10 years). Twenty-two subjects were males and 4 were females. Eighteen subjects were white, 5 were black, and 3 were Hispanic. All knew that they would be detoxified with either clonidine or methadone and that they would be randomly assigned to one or the other treatment on a double-blind basis with an equal probability of receiving either treatment.

Nineteen of the 26 subjects were enrolled in a methadone maintenance treatmant program for at least 6 months before entering the study and were receiving a daily methadone dose of 15 to 30 mg. The remaining 7 subjects were using illicit opiates (heroin and/or methadone) and not enrolled in any treatment program upon admission to our outpatient clinic. These subjects were stabilized on a daily methadone dose of 15 to 30 mg for at least 3 weeks before entering the study. When the detoxification procedures were initiated, 18 subjects were receiving 20 mg methadone, 3 were receiving 30 mg, 3 were receiving 15 mg, and 2 were receiving 25 mg.

Upon entering the study, subjects were randomly assigned to the clonidine or methadone detoxification procedure. The procedures were conducted under double-blind placebo-controlled conditions in which all subjects received both liquid medication (methadone or placebo) and tablet medication (clonidine or placebo) on each study day. In the clonidine procedure, patients received active clonidine and placebo methadone. In the methadone procedure, patients received placebo clonidine and active methadone, A comparison of the subjects assigned to the clonidine and methadone groups indicated that the randomization process yielded compararable subject samples with respect to several relevant psychosocial, demographic, and drug use variables.

The clonidine detoxification procedure consisted of abrupt discontinuation of active methadone and simultaneous introduction of active clonidine. The methadone detoxification procedure consisted of meththadone dose reductions of 1 mg per day until a zero dose was reached, with simultaneous administration of placebo clonidine. Clonidine dose regimens were individualized on a double-blind basis according to dosing methods described previously (Washton et al., 1980b). The initial clonidine dose regimen consisted of 0.1 mg every 4 to 6 hours as needed for withdrawal discomfort. The total daily dose was then increased, as needed, by 0.1 mg or 0.2 mg increments on succeeding days in an attempt to minimize withdraw discomfort without generating untoward side effects. In some cases, clonidine doses were held steady or decreased to compensate for sedation and/or hypotension. The total daily clonidine dose did not exceed 1.2 mg on any given day. Most subjects received night-time sedative medication to alleviate insomnia.

At each clinic visit (3 to 5 times per week) subjects met with the investigators for review of withdrawal symptoms, medication effects, and compliance with suggested clonidine dose regimens. Neither the subjects nor investigators were told whether the subject had been assigned to the clonidine or methadone procedure. Blood

pressure and pulse rate were recorded at each clinic visit, but by someone other than the investigators, because clonidine's observable effects on these measures would violate the double-blind, Subjects were free to terminate their participation in the study at any time and be restabilized on methadone.

The datum of primary interest in this study was a comparison of detoxification success rates with the clonidine and methadone procedures. "Detoxification success" was operationally defined as completion of a 10-day opiate-free period following discontinuation of active methadone. Opiate-free status was evaluated by laboratory analysis of supervised urine samples and additionally, in subjects who desired naltrexone treatment, by a naloxone challenge of 2.0 mg i.v. which served as the necessary screening procedure before starting naltrexone.

Since the methadone detoxification procedure was conducted at a fixed rate of 1 mg per day, the number of days from initiation of the procedure to zero dose varied according to the subject's starting methadone dose, with a subsequent fixed 10-day post-methadone period required to complete the detoxification procedure. Thus, for subjects on a 20 mg starting dose, completion of the procedure required 30 days. In order to maintain double-blind conditions, the length of the clonidine procedure was extended to be identical with that of the methadone procedure and, therefore, was also determined by starting methadone dose plus 10 additional days. Although all clonidine subjects could potentially achieve the 10-day post-methadone criterion by day 10 of the study, irrespective of starting methadone dose, the medications were continued according to protocol until the defined study endpoint. All subjects were informed that completion of the study procedures with a 10-day opiate-free period would be a necessary prerequisite to any post-detoxification treatment with or without naltrexone.

RESULTS

Table 1 presents a group comparison of detoxification success rates in terms of subjects' ability to achieve a 10-day opiate-free period following discontinuation of active methadone. For the clonidine procedure, the data represent subjects' status on day 10 and for the methadone procedure they represent subjects' status at the defined endpoint of the study which, in most cases, was day 30. These data show an overall success rate of 38% for the subject sample as a whole, with no statistically significant difference between the clonidine and methadone procedures. Examination of individual-subject data revealed no association between ability to detoxify and subject's age, years addicted, employment status, or starting methadone dose.

Two of the 4 clonidine subjects who achieved the opiate-free criterion by day 10 subsequently relapsed to opiate use before completion of the double-blind procedure on day 30. Eleven of the 3 methadone subjects reached a zero methadone dose, although 5 of the 11 subsequently relapsed to opiate use during the final 10-day post-methadone period.

TABLE 1

SUCCESS IN ACHIEVING 10 DAYS OPIATE-FREE
(N=26)

	Successful		Unsuccessful	
	%	(N)	%	(N)
TOTAL SUBJECT SAMPLE (N=26)	38%	(10)	62%	(16)
Clonidine Procedure (N=13)	31%	(4)	69%	(9)
Methadone Procedure (N=13)	46%	(6)	54%	(7)

Chi-square test: p > .05.

Consistent with our previous findings (Washton et al., 1980a; 1980b), patients given the active clonidine treatment found that it relieved a substantial portion of their withdrawal discomfort. Lethargy and sluggishness were the most consistent complaints. During induction onto clonidine, patients occasionally experienced transitory episodes of mild dizziness or lightheadedness which tended to abate with continued clonidine administration over the course of several days.

Methadone subjects assumed that they were receiving the active clonidine treatment because they attributed the relative absence of withdrawal symptoms during most of the detoxification procedure to effectiveness of the placebo tablets. Clonidine subjects, on the other hand, reported sedative effects not reported by those on the placebo tablets. Thus, although doubleblind conditions could not be strictly maintained, all subjects were operating under the assumption that they were receiving the active clonidine treatment.

Of the 8 subjects who were opiate-free at completion of the study, 6 began treatment with naltrexone and 2 elected to continue in drug-free treatment without naltrexone. Of the 18 subjects who failed to complete detoxification, 17 were restabilized on methadone and 1 was lost to follow-up.

The slightly lower success of the clonidine procedure did not appear to be due to less effective control of withdrawal discomfort. The major syptomatic complaints were identical for both subject groups (i.e., lethargy, restlessness, and insomnia) and subjective ratings of symptom severity were indistinguishable as well. Moreover, most subjects who discontinued their detoxification attempt felt that it was not primarily a result of physical withdrawal discomfort. Of the 18 subjects who discontinued, 8 stated that they returned to opiates in response to some form of psychological stress (e.g., relationship problems, job pressures, dysphoric feeling state) and 6 subjects attributed their relapse to an uncon-

trollable craving for opiates that was not associated with an identifiable precipitating event. Four subjects, 2 in the clonidine group and 2 in the methadone group, felt that physical withdrawal discomfort was the primary reason for discontinuing their detoxification attempt. Thus, the present observations appear to indicate that the clonidine and methadone procedures generated roughly equivalent levels of withdrawal symptomatology.

There was a noticeable difference between groups, however, with respect to the point at which withdrawal symptoms emerged. Clonidine subjects reported symptoms during the first week of the study whereas methadone subjects reported symptoms during the final week. In both cases, the emergence of symptoms followed discontinuation of active methadone.

DISCUSSION

Our findings indicate that the clonidine and methadone detoxification procedures employed in this study were of comparable efficacy in helping patients achieve a 10-day opiate-free period. There was no statistically significant difference between the two procedures in terms of detoxification success rates, although success with the clonidine procedure was slightly lower than that of the methadone procedure.

It appears that the clonidine detoxification procedure was selectively disadvantaged in the current protocol by having to artificially extend the length of the procedure simply to maintain double-blind conditions. In our open studies (Washton et al., 1980a; 1980b), patients found clonidine to be a highly desirable treatment primarily because it allowed them to detoxify in the shortest possible time. Within only 10 days after discontinuing methadone, patients were able to begin naltrexone or drug-free treatment. Knowing that the detoxification would be completed within such a short period of time seemed to help them endure withdrawal discomfort and control urges to use opiates. By contrast, in the present study, the detoxification procedure was considerably longer and, in most cases, lasted 30 days, Since clonidine subjects became symptomatic during the first week of the study, a 30-day period was perceived as a rather long period of time to endure even mild withdrawal discomfort without giving in to urges and cravings for opiates. The long time period from onset of withdrawal symptoms to completion of the detoxification procedure actively discouraged patients from continuing in the study despite our intensive efforts at fostering their retention. In the methadone procedure, on the other hand, patients became symptomatic only toward the end of the procedure and, similar to patients in open clonidine treatment, knowing that completion of the detoxification was almost at hand, helped them to persevere.

Thus, clonidine might be maximally efficacious when used as a rapid detoxification treatment. A more appropriate test of its efficacy would be a double-blind comparison of clonidine vs. placebo for 10 days following abrupt discontinuation of low-dose

methadone. Another possibility would be an open parallel-groups study where subjects are randomly assigned to either a 10-day clonidine detoxification procedure or a gradual methadone dose reduction procedure similar to that employed in the present study.

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ACKNOWLEDGEMENTS

This research was supported in part by grant No. 1R01 DA 02405-01 from the National Institute on Drug Abuse. The authors are grateful to Dorothy Singletary, R.P.A., and Joseph F. Perzel, Jr., Psy. D., for assisting with the conduct of the research.

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Clinical Utility of Clonidine in Opiate Withdrawal

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INTRODUCTION

We have reported that a single dose of 5 ug/kg of clonidine but not placebo caused a rapid and significant decrease in acute opiate withdrawal signs and symptoms inpatients addicted to methadone, other synthetic opiates, and heroin (1-3). These initial studies suggested a new use for clonidine as a nonopiate treatment for rapid opiate detoxification (4). In addition these studies with the alpha-2 adrenergic agonist clonidine which reduces brain norepinephrine activity support a noradrenergic hyperactivity hypothesis for opiate withdrawal (5).

While our previous inpatient studies (1-3) offered considerable Promise they were complicated by the small number of patients studied. We now have given clonidine acutely in a dose of 6 ug/kg and chronically in a dose of 17 ug/kg/day in an inpatient setting to 100 opiate addicts after withdrawal from 10-80 mg of chronic methadone treatment.

SUBJECTS AND METHODS

Subjects were patients who had been addicted to opiates for up to fifteen years. They all expressed interest in discontinuing methadone and gave informed consent to a study which required an abrupt withdrawal from methadone three days after admission to the Evaluation and Research Unit and at least 36 hours with no opiate administration. All patients had previous unsuccessful attempts at detoxifying from opiates. All had objective signs of opiate withdrawal. Patients were observed for the presence or absence of withdrawal signs and symptoms by a research nurse clinician every hour from 8:00 a.m. while the patients were at bed rest during the day of clonidine administration (1). The nurse rated twenty-one items, associated with withdrawal (1) as present or absent, the total score being added to give a measure of withdrawal severity. The symptoms and signs were opiate craving, anxiety, yawning, perspiration, lacrimation, rhinorrhea, yen sleep, mydriasis, goose flesh, tremors, hot and cold flashes, aching bones and muscles, anorexia,

increased blood pressure, insomnia, increased temperature, increased respiratory rate and depth, increased pulse rate, restlessness, nausea and vomiting, and diarrhea. After the first day of clonidine administration, the patients were administered clonidine 17 ug/kg/day in divided doses and rated three times a day before clonidine administration for opiate withdrawal symptoms by a research nurse clinician. In addition, all patients completed self-rating analog scales. These analog rating scales were utilized to assess for changes in nervousness, being high, unpleasantness, energy, irritability, fear and anger. They were completed every hour from 9:00 a.m. during three times a day prior to clonidine administration. On the first day, the patients took 6 ug/kg of clonidine or placebo orally in matching vehicles to demonstrate the effect of clonidine on opiate withdrawal signs and symptoms and to assess the changes in blood pressure produced by this dose of clonidine. After the initial clonidine and placebo administration, patients without precipitous blood pressure declines were given clonidine 17 ug/kg/day for at least nine days. Clonidine dose was gradually decreased to zero by day fourteen. Naloxone (1.2 mg) was given intravenously to assess for Naltraxone readiness. All patients were excluded who had a previous history of cardiac arrhythmias, hypotension, vasomotor instability, psychiatric illness or hospitalization (6).

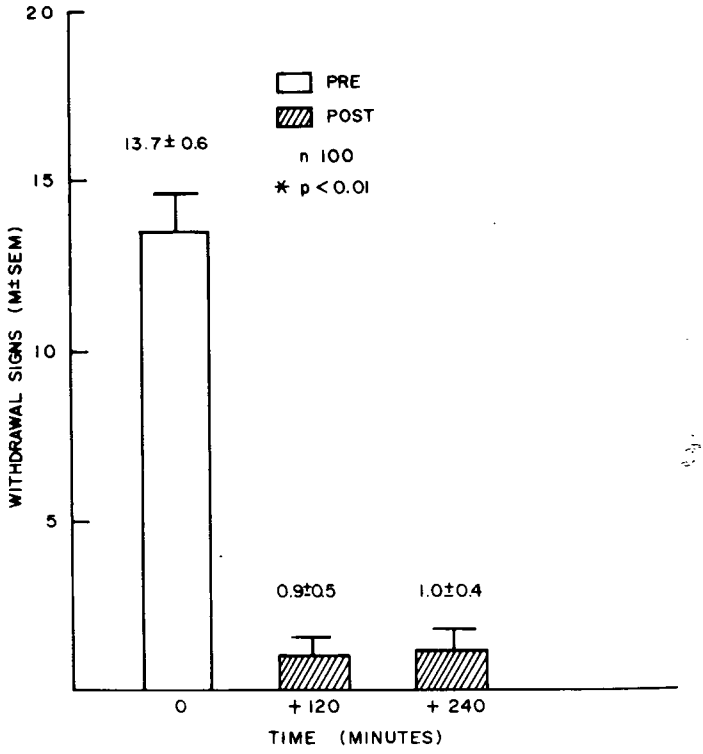
RESULTS

Acute First Dose Study

The number of opiate withdrawal signs increased during the baseline period. Clonidine 6 ug/kg produced a rapid and significant decrease in opiate withdrawal signs and symptoms to 0.9±0.5 at 120 minutes (paired t test $p<0.01$). Opiate withdrawal ratings remained unchanged for an additional 240 minutes. Systolic and diastolic blood pressure was significantly reduced at 120 minutes after clonidine administration ($p<0.01$). Blood pressure was not significantly changed over the next 240 minutes. Relief of subjective and objective distress was significant.

On self-rating analog scales where 70 is the highest score, there were significant ($p<0.01$) decreases in self-rated nervousness, irritability, "uninvolved" and "angry" scales at 120 minutes. There were no significant changes noted in self-rating analog scales for energy or feeling "high." Placebo had no significant effects on any of the above measurements or ratings. The effect of clonidine was not significantly different for those patients addicted to low or moderate doses of methadone.

Figure 1



All 100 patients were continued on clonidine in an inpatient hospital setting. None of the patients chose a return to methadone after their first dose of clonidine. On the first day of clonidine administration, the patients were given 6 ug/kg as a test dose and then 6 ug/kg at bedtime. Thereafter, 17 ug/kg/day of clonidine was given in divided doses of 7 ug/kg at 8:00 a.m. and 3 ug/kg at 4:00 p.m. and 7 ug/kg at 11:00 p.m. Each day vital signs and nurses' abstinence ratings and self-ratings were done as described previously (1-3). Clonidine doses were withheld in some cases due to severe hypotension. Additional clonidine was given, if needed. There were no significant changes in the abstinence ratings during this ten-day inpatient trial. The majority of patients, however, complained of difficulty in falling asleep. Dry mouth, sluggishness, depression and occasional bone pain were more infrequent complaints. Systolic and diastolic blood pressure remained significantly decreased throughout the nine days of 17 ug/kg of clonidine administration. There were no significant increases or decreases in self-rated nervousness, irritability, uninvolved, angry, fear, "high" or energy. Clonidine dose was decreased to compensate for oversedation or hypotension. On days 11,12,13 the clonidine dose was decreased by 50%. On day 14, the patients received no clonidine whatsoever. None of the

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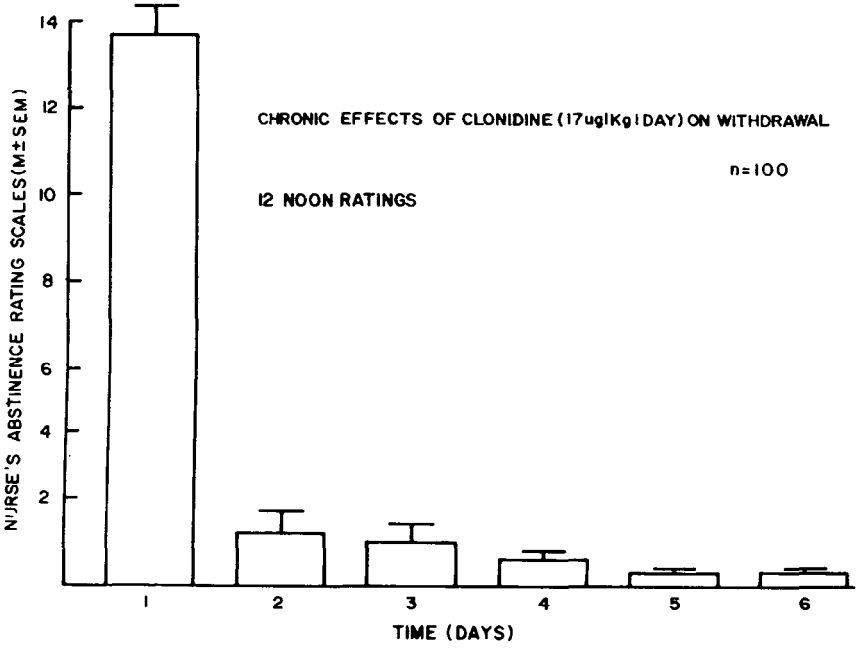
Figure 2



patients showed any increase in opiate withdrawal signs or symptoms or had the emergence of clonidine withdrawal symptoms using this protocol. One patient eloped from the hospital on day 5 of the study. On day all patients were given Naloxoma (1.2 mg) intravenously to assess for residual opiates or dependence. All Naloxone test responses were negative. Ninety-nine of the 100 patients completed the 14-day inpatient study and were Naltrexon-ready.

DISCUSSION

As compared to our previous studies (1-4) the data reported here were not confounded by small sample size, difficulties in compliance and other drug use. All patients in this study were successfully detoxified from chronic methadone addiction in an inpatient setting and all but one were fourteen or more days without any opiate administration at the time of discharge from the hospital. This detoxification success rate is much greater than our experience or data reported in the literature for methadone detoxification groups. Clonidine could be given in high enough doses to reverse all opiate withdrawal signs and the resultant significant and potentially serious decreases in systolic and diastolic blood pressure were successfully managed in the hospital. Finally, the risk of illicit drug adding to the hypotensive effects of clonidine was prevented in this inpatient study.

In this inpatient detoxification study, we have shown that clonidine is a safe and effective non-opiate treatment for opiate withdrawal

which suppresses the symptoms and sighs of opiate withdrawal as well as the affective changes associated with opiate withdrawal. Affects associated with withdrawal such as anxiety, irritability and anger were rapidly reduced after clonidine administration. Clonidine is therefore extremely useful as a noneuphorogenic treatment for detoxification. Some of the advantages of clonidine detoxification are listed in Table 1. This 14-day inpatient clonidine detoxification protocol could be useful in the treatment of selected opiate addicts. For example, clonidine detoxification could be linked to maintenance on long acting opiate antagonists such as Naltrexone. Clonidine, being a nonopiate, allows the patient to abruptly discontinue opiate administration and opiate-free long enough to initiate maintenance treatment with Naltrexone. Clonidine detoxification my allow the detoxification of patients maintained on methadone who have had previous unsuccessful attempts to detoxify due to the norbidity of current slow detoxification practices. Clonidine is also potentially useful in the treatmant of iatrogenic addictions and the protracted abstinence syndrome where the risk of exposure toopiates might be reduced. Clonidine appears most useful in the treatment of working patients, iatrogenic addictions, nondrug-using methadone maintenance patients, patients with family and work support systems who are also good candidates for Naltrexone.

Table 1

1. Rapid
2. Nonopiate
3. Noneuphoria-producing
4. High success of inpatient detoxification
5. High success of Naltrexone induction
6. Provide drug-free or Naltrexone alternative to methadone maintenance, for:
   a. Iatrogenic addictions
   b. Pill, cough medicine, "nonstreet" opiate addiction
   c. Suburban addict with no previous exposure to clinic-related drug abuse and crime
7. Ideally suited for the working addict
8. Enhance the role of M.D. and M.D.-patient relationship
9. Define and limit the role of maintenance methadone

In summary, the effects of clonidine on opiate withdrawal in man (1-4,9) and rodent (5,7,8) provide pharmacogical support for a noradrenergic hyperactivity hypothesis for opiate withdrawal and suggest that clonidine reverses opiate withdrawal by replacing opiate-mediated inhibition with alpha--2 adrenergic and opiate re ceptors, my become activated in opiate withdrawal-related panic states and possibly naturally occurring panic states.

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Clonidine Hydrochloride Detoxification From Methadone Treatments: The Value of Naltrexone Aftercare

R. A. Rawson, A. M. Washton, R. B. Resnick, and F. S. Tennant, Jr.

At the past two meetings of the Committee on Problems of Drug Dependence, data have been presented which indicate that clonidine hydrochloride can be effective in alleviating opiate withdrawal symptoms (Gold, Redmond and Kleber, 1978a; Washton, Resnick, and Rawson, 1980a). These presentations and a number of recently published reports (Gold, Redmond and Kleber, 1978b; Washton, Resnick and Rawson, 1980b) have aroused substantial public interest in developing clonidine as a treatment for relieving opiate withdrawal symptoms. Although the extent of clonidine's clinical usefulness has not yet been determined, it is already apparent that clonidine is uniquely suited for one purpose which no other opiate detoxification agent can adequately address. Since it is not an opiate, clonidine is precisely the type of drug needed for the rapid detoxification of patients from opiates prior to their induction onto the narcotic antagonist, naltrexone. A review of the work on naltrexone indicates that one of the limiting factors in the use of the drug has been the inability of patients to become sufficiently opiate free prior to induction onto the medication. In addition, some of the high early dropout rates from naltrexone treatment may have been due to patient discomfort from mild precipitated withdrawal symptoms resulting from incomplete prenaltrexone detoxification.

If clonidine can be developed as a viable prenaltrexone detoxification agent, the usefulness of naltrexone treatment may be greatly enhanced. This possibility is supported by data presented in the Washton and Resnick paper in this volune, which indicates that 72 percent of the methadone maintenance patients detoxified with clonidine successfully were inducted onto naltrexone. This is a substantial improvement over prior prenaltrexone detoxification methods. For example, in Leo Hollister's summary of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists, only 21 percent of those methadone maintenance patients who volunteered for naltrexone treatment took an initial dose of the medication.

The efficacy of clonidine to relieve opiate withdrawal symptoms to such a degree that the transition from methadone to naltrexone is accomplishable raises a further question. If clonidine can relieve withdrawal symptoms to such a degree that patients can achieve the 10-day opiate-free period necessary to start naltrexone, is it possible that the methadone to drug free transition can be made without the intermediate step of naltrexone treatment? If opiate withdrawal symptoms can be relieved substantially during the initial postmethadone period, the naltrexone step may be unnecessary in progressing from methadone treatment to drug free status.

The purpose of this study is to evaluate the usefulness of naltrexone aftercare following clonidine detoxification from methadone maintenance treatment. This paper contains data from a collaborative study between New York Medical College and Community Health Projects in West Covina, California.

METHOD

Subjects and Setting

Subjects were selected from two methadone maintenance clinic populations. Subjects in the clonidine/naltrexone group were selected from volunteers at the New York Medical College Division of Drug Abuse Research and Treatment. Subjects in the clonidine only group were selected from volunteers at the Community Health Projects clinics located in the San Gabriel Valley, 30 miles east of Los Angeles. All subjects had at least a two-year history of opiate use and were over 18 years of age.

Obviously, the results of the clonidine only versus clonidine/ naltrexone group comparison must be interpreted cautiously in view of the corresponding California - New York difference. However, two considerations mitigate the importance of the location difference. First, as can be seen from Table 1, there were no significant differences between the subject samples on a variety of important demographic, psychosocial and drug history variables. Second, the senior author (Rawson) was involved with the coordination of the study in both sites. All data collection instruments and clonidine treatment procedures were identical for subjects in both groups. All subjects entering treatment in both groups sought out treatment due to their desire to detoxify with clonidine. Most of the subjects had never heard of naltrexone and many in the clonidine/naltrexone group were initially sceptical of the need for naltrexone aftercare.

Procedure

At the time of the intake interview, demographic, psychosocial and drug history data were collected from all subjects. In a subsequent interview with the study coordinator (Rawson) a description of the clonidine detoxification program was presented

to each subject and the clonidine informed consent forms were signed. In addition, subjects in the clonidine/naltrexone group were presented information about naltrexone and required to sign a naltrexone informed consent form. Subjects in the clonidine/naltrexone group were informed of the necessity of achieving a 10-day opiate-free period in order to start naltrexone with no precipitated withdrawal symptoms. Subjects in the clonidine only group were informed that the 10-day opiate-free period was extremely important if they were to successfully accomplish their detoxification from methadone and achieve opiate abstinence. Subjects were subsequently treated in an identical manner throughout the clonidine detoxification procedure.

The detoxification was initiated with an abrupt switch from methadone to clonidine. The dose was adjusted for each patient so as to maximize therapeutic benefit and minimize the occurrence of adverse side effects such as sedation and orthostatic hypotension. Similar amounts of clonidine were used for subjects in both groups. Ten days after opiates were discontinued, a naloxone challenge of 1.2 mg was administered to confirm opiate-free status. For subjects in the clonidine/naltrexone group, a negative naloxone challenge also provided the necessary screening procedure to determine readiness for naltrexone induction. On the day following the naloxone challenge clonidine doses were gradually reduced by 0.1 or 0.2 mg decrements per day until a zero dose was reached. While on clonidine, subjects were seen 5 days per week for a recording of withdrawal symptom ratings, blood pressure, medication adjustments and a self-report of drug use.

At the completion of their detoxification, subjects in the clonidine only group were encouraged to stay in drug free psychotherapy offered at the same facility or accept referrals to a residential program. Subjects in the clonidine/naltrexone group were encouraged to stay in postdetoxification treatment with naltrexone which required three clinic visits per week. Naltrexone treatment consists of 100 mg doses of naltrexone on Monday and Wednesday and a 150 mg dose on Friday. None of the subjects at either facility were engaged in counseling or psychotherapy during the detoxification period.

RESULTS AND DISCUSSION

The primary question addressed by this study is whether naltrexone aftercare facilitates the success of clonidine detoxification from methadone maintenance. "Detoxification Success" is operationally defined by the following criteria:

1. The completion of a 10-day opiate-free period following discontinuation of methadone; and
2. The opiate use status of subjects 30 days postmethadone.

Clonidine Detoxification Period (last day of methadone to day 10 postmethadone)

Table 2 presents a group comparison of "success rates" of subjects regarding their ability to achieve a 10-day opiate-free period following the discontinuation of methadone maintenance treatment. As can be seen from this table, 9 of 12, or 75 percent of those subjects in the clonidine/naltrexone group achieved the 10-day opiate-free criterion, while only 3 of 12 or 25 percent of the clonidine only group were successful (X^2 = 6.0, df=1, P<.05). These data suggest that the availability of naltrexone on day 10 postmethadone affects the success of a clonidine detoxification procedure on days 1-9 postmethadone. One explanation for this finding is that although both groups of subjects were nearly identical on a broad range of pretreatment variables, it is possible that the clonidine was simply less effective in relieving the withdrawal symptoms of subjects in the clonidine only group.

This explanation appears unlikely since the symptoms rating data collected from subjects were extremely similar at both facilities. Specifically, subjects in both groups found clonidine to be: extremely useful in relieving physical and autonomic signs of withdrawal; moderately useful in relieving anxiety, restlessness and insomnia; and not useful in relieving anergia. Other evidence to suggest that clonidine was successful in reducing the severity of withdrawal symptoms was that few of the subjects in either group prematurely terminated their detoxification due to unacceptable levels of withdrawal discomfort. Table 3 lists the reasons given by the 12 subjects who discontinued their detoxification when asked why they had decided to stop. As is shown in this table, most of the subjects experienced extreme opiate craving as well as problems at work and at home, but few of the subjects reported that unacceptably high levels of withdrawal symptoms were instrumental in the discontinuation of their detoxification.

The differential efficacy of the clonidine detoxification procedure between the two groups of subjects does not appear to have been a result of differential symptom relief; rather, it appears to have been the result of different subject attitudes toward their detoxification. Subjects in the clonidine/naltrexone group perceived the clonidine detoxification as a transitional treatment with a specific goal. Naltrexone induction on day 10 postmethadone was perceived as a clear endpoint to the detoxification. Subjects in this group frequently expressed the feeling that they had "made it" when they started naltrexone and many reported feeling relief that once on naltrexone they no longer had to struggle with the urges and cravings to use opiates. It appeared that if the clonidine procedure was perceived by subjects as being for a specific number of days with a clear goal and endpoint such as starting naltrexone, most of them could exert sufficient control to abstain from opiate use for the 10 days post methadone.

Subjects in the clonidine only group did not appear to view the detoxification process as having a clear endpoint. Although they were told that a 10-day opiate-free period was necessary, 9 of 12 were not able to achieve this 10-day abstinence period. As previously noted the return to opiate use was not attributed to withdrawal symptom relief but rather to an inability of subjects to resist opiate urges and cravings.

Postdetoxification Period (Day 10 to Day 30 postmethadone)

Table 4 presents the opiate use status of subjects in the two groups on day 30 postmethadone. As shown in the table, 7 of 12 of the clonidine/naltrexone group subjects were on naltrexone and/or opiate free on day 30, while only 2 of the 12 clonidine only group subjects were opiate free ($X^2 = 4.42$, df=1, $P<.05$).

These data strongly support the contention that naltrexone can be extremely useful in preventing readdiction to opiates during the initial postmethadone period. Additionally, these data should serve as a caution to those who may have unrealistic expectations about the role of clonidine in addiction treatment. Patient anecdotal reports and symptom rating scores strongly suggest that clonidine will provide substantial relief from opiate withdrawal symptoms. However, for patients who do find clonidine useful, it is useful only as part of a comprehensive treatment plan with a clearly defined aftercare program. The expectation that several weeks of clonidine treatment will provide a sufficient postmethadone treatment is not supported. It is clear that during the initial postmethadone period patients are extremely vulnerable to readdiction even with the benefit provided by clonidine.

SUMMARY

From the data collected in this collaborative New York Medical College - Community Health Projects study, the following conclusions are possible.

1. Based upon subject reports and symptom rating data, clonidine hydrochloride provided substantial relief from opiate withdrawal symptoms. The degree of symptom-relief and the cluster of symptoms most improved appeared similar for both groups of subjects.

2. The availability of naltrexone aftercare significantly increased the success rates of subjects in achieving a 10-day opiate-free period following the discontinuation of methadone.

3. The relapse to opiate use during the clonidine detoxification period was reported by most subjects to be the result of extreme opiate craving brought on by environmental and psychosocial variables, rather than a response to severe withdrawal symptoms.

4. The induction onto naltrexone provided a tangible endpoint to the detoxification process. Subjects who viewed the detoxification process in this manner appeared to be better able to control their impulses to use opiates.

5. The availability of naltrexone aftercare significantly improved the 30-day postmethadone followup results. A significantly higher percentage of those subjects in the naltrexone group were opiate free at the 30-day followup point than were subjects for whom naltrexone was not available.

TABLE 1
PRETREATMENT SUBJECT CHARACTERISTICS

	Clonidine Only Group	Clonidine/ Naltrexone Group
Mean Age	31	30
Mean Years Addicted	9.7	10.1
Male/Female Ratio	11/1	10/2
Anglo/Black or Hispanic	9/3	7/5
Mean Methadone Maintenance Dose	44 mgs.	41 mgs.
Mean Methadone Dose When Switched to Clonidine	22.3	20
Percent Employed	58%	50%
Percent in a Relationship	90%	75%
Percent Who Bad Used Illicit Opiates During Month Prior to Detoxification	66%	58%

TABLE 2
SUBJECTS SUCCESSFULLY ACHIEVING
TEN DAYS OPIATE FREE

	Number Successful	Number Unsuccessful
Clonidine Only Group	3	9
Clonidine/Naltrexone Group	9	3

$X^2 = 6.0$, DF = 1, $P<.05$

TABLE 3
REASONS CITED FOR RETURN TO OPIATE USE*

	Number of Subjects Reporting Problem
Extreme Craving for Opiates	7
Coping with Employment-Related Stress	5
Coping with Family/Interpersonal Problems	7
Relief from Depression	3
Relief from Boredom	3
"Someone Came By With Heroin"	2
Relief from Withdrawal-Related Insomnia	2
Relief from Withdrawal/Clonidine Related Anergia	2
Relief from All Other Withdrawal Symptoms	1

*Some Subjects Cited More Than One Reason

TABLE 4
SUBJECT STATUS 30 DAYS POSTMETHADONE

Status	Clonidine Only Group	Clonidine/ Naltrexone Group
Opiate Free, In Postdetoxification Treatment (includes naltrexone)	0	6
Opiate Free, Not In Treatment	2	1
Returned to Methadone Maintenance	5	3
Using Illicit Opiates	5	2
Total	12	12
Summary*		
Opiate Free	2	7
Not Opiate Free	10	5

* $x^2 = 4.42$, DF = 1, $P<.05$

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Psychotherapy and Naltrexone in Opioid Dependence

R. B. Resnick, A. M. Washton, N. Stone-Washton

An issue of current importance to psychiatry is the efficacy of psychotherapy and phamacotherapy in comparison to one another and in combination. In addiction treatment, the importance of individual counseling for the successful use of opioid antagonists such as naltrexone has often been suggested but as yet there is insufficient data to support this contention. Furthermore, naltrexone efficacy studies have not controlled for the type or degree of patients' involvement in interpersonal aspects of treatment. The present pilot study evaluated the effectiveness of naltrexone in conjunction with a high intervention treatment that included individual counseling as compared with a low intervention treatment that excluded such counseling.

METHOD

Sixty-six opioid-dependent volunteers were randomly assigned at intake to either a low intervention (N=31) or high intervention (N=35) treatment group. All subjects were over 18 years of age, had been addicted to opiates for at least one year, were free of serious medical and psychiatric illness and signed an informed consent. An attempt was made to match the two groups for level of opioid dependence immediately prior to entering the study and number of subjects who entered the study from long-term methadone maintenance as compared with those who entered with dependence on illicit opioids (street addicts). All subjects were new admissions to the treatment unit since it was felt that a prior treatment history at this facility would confound their assignment to groups.

Because naltrexone treatment has been limited by high drop-out rates before subjects even received the first naltrexone dose, subjects were assigned to their treatment group prior to detoxification in order to assess whether the intervention level would affect naltrexone induction rates. The detoxification period also seemed to be an opportune time to initiate a therapeutic relationship with subjects in the high intervention group.

All subjects were offered identical medical and nursing services which included detoxification from opioids followed by maintenance on naltrexone requiring three clinic visits per week. Each high intervention subject was additionally offered regularly scheduled psychotherapy sessions with an experienced therapist who closely monitored the patients' clinical course and was available to provide a variety of services. The therapy included supportive, directive and insight-oriented techniques, depending on the orientation of the therapist, the needs of the patient, and what seemed to be most helpful at a particular point in time. In addition to offering at least one scheduled therapy session each week, the therapist maintained a high level of availability to assist with problems that my have emerged between the scheduled sessions. Therapists encouraged patients to contact them at the clinic or at home if there was a need for services outside the scheduled visits. Subjects were telephoned by therapists whenever they failed to appear for a scheduled clinic visit. In general, therapists made an active attempt to provide patients with continuing emotional support and develop a strong therapeutic alliance.

Low intervention subjects were assigned a case manager who provided only concrete services, referral to outside agencies, or crises intervention. The case managers were instructed to avoid engaging patients in a therapeutic relationship, i.e., no attempt was made to encourage discussions about personal problems or to contact subjects when a clinic visit was missed, Low intervention subjects requesting psychotherapy were referred to community agencies or private practitioners who could provide such services. In all cases an attempt was made to service the needs of low intervention subjects without promoting a close personal bond between the subject and staff members.

The frequency and duration of contacts with the staff were recorded for each subject. The contacts were classified as either: (1) Medical/Data Collection contacts, or, (2) counseling contacts. Contacts with the physician that primarily addressed medication issues, physical examinations and symptoms or with the project coordinator for obtaining data on mod or psychosocial functioning were designated Medical/Data Collection contacts. Contacts with the therapist, case manager or nurse that primarily concerned other issues were designated Counseling. For high intervention subjects counseling included formal therapy sessions as well as telephone and other contacts that provided advice, encouragement, or support on an informal basis. For low intervention subjects, Counseling contacts consisted of discussion about referrals to outside agencies or time spent providing crisis intervention.

Outcome evaluations were made with respect to: 1) detoxification success rates; 2) naltrexone retention rates, and 3) opiate use status at three and six months following the first naltrexone dose.

RESULTS

Table 1 shows that before entering the study the high and low in-

tervention subjects were comparable with respect to several key demographic, psychosocial, and drug use variables,

TABLE 1

DEMOGRAPHIC AND DRUG HISTORY VARIABLES FOR

HIGH vs. LOW INTERVENTION GROUPS

	High Intervention (N=35)	Low Intervention (N=31)
Sex		
Male	66%	71%
Female	34%	29%
Ethnicity		
black	26%	29%
Hispanic	8%	3%
white	66%	68%
% Employed	49%	52%
% in significant interpersonal relationship	66%	76%
Mean Age (years)	28.5	29.8
Years Addicted	7.8	9.0
Longest Opiate-Free Period	8 months	13 months
Longest Period Employed	3.3 years	3.3 years
Level of Dependence		
Street Addictson Heroin	$67/day	$55/day
Street Addicts on Methadone	36 mg	38 mg
Methadone Maint. Patients	30 mg	41 mg

The contact time data shown in Figure 1 indicates that although both groups received almost the same amount of time over medical issues and data collection, the high intervention group spent significantly more time with their therapist discussing interpersonal problem and issues concerning psychosocial functioning. Counseling contact time for high intervention subjects averaged about 70 minutes per week throughout the study. For low intervention subjects counseling time averaged less than 20 minutes per week during detoxification and then dropped to less than half that time until treatment termination. For both high and low intervention groups there was an average of 45 minutes per week in Medical/Data Collection contacts during the early phase of treatment, when all subjects were seen for 10-15 minutes 3-5 times a week for symptom review and medication adjustments.

FIGURE 1

MEAN WEEKLY CONTACT TIME BETWEEN THE SUBJECTS AND STAFF FOR HIGH vs. LOW INTERVENTION GROUPS

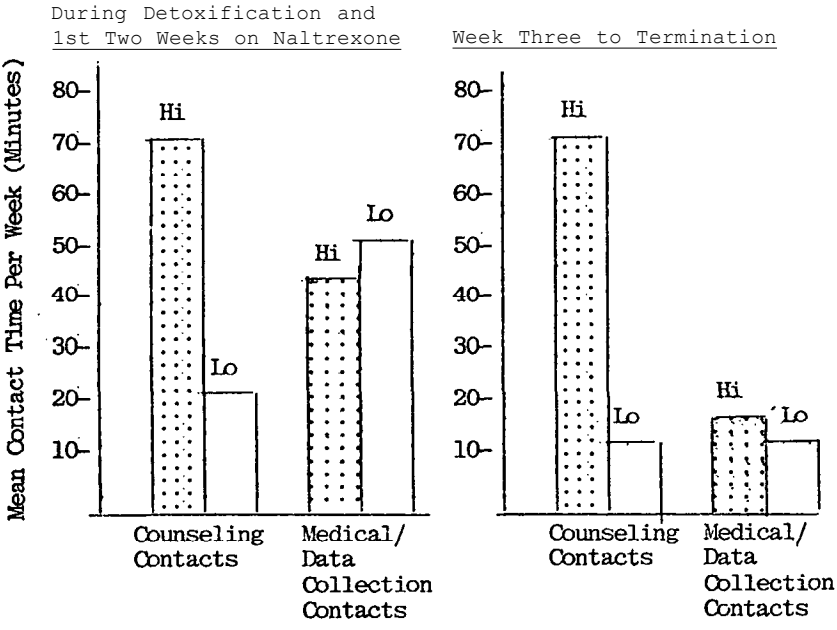

FIGURE 2

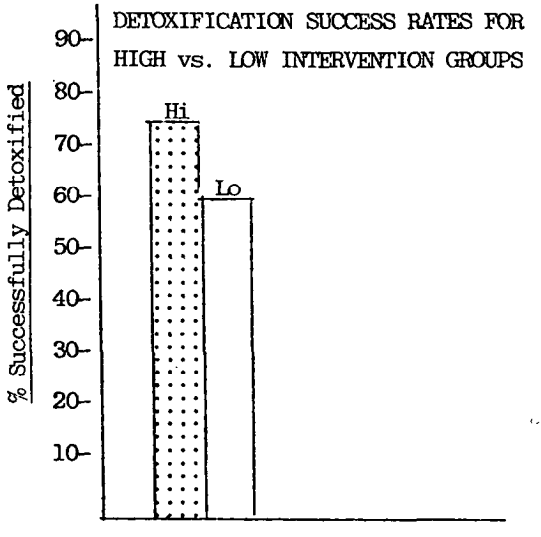

Figure 2 compares detoxification success rates (i.e., naltrexone induction rates) for the high and low intervention subjects. High intervention subjects showed greater detoxification success rates than low intervention subjects (73 percent vs. 57 percent) although this difference was not statistically significant (> .05).

Table 2 compares time on naltrexone for the two treatment groups. High intervention subjects tended to remain on naltrexone for a longer period of time and this finding was statistically significant for subjects who detoxified from illicit opioids but not for those who entered the study from methadone maintenance. Illicit opioid users who received the high intervention treatment remained on naltrexone an average of 9.3 weeks and as long as 26 weeks, whereas those who received the low intervention treatment remained on naltrexone an average of only 2.1 weeks and no longer than 7 weeks. These findings are also depicted graphically in Figure 3 which shows attrition rate curves for the two groups over the first 26 weeks.

The bar graph in Figure 4 shows the percentage of subjects still opiate-free at three and six months after starting naltrexone and indicates a greater likelihood of opiate-free status for subjects in high intervention treatment: 73 percent vs 40 percent at 3 months and 54 percent vs. 40 percent at six months follow-up, Of those patients who were opioid dependent at follow-up, 70 percent from the high intervention group had entered methadone maintenance treatment and 30 percent were using illicit opioids, whereas only 33 percent from the low intervention group had entered methadone maintenance and the remaining 67 percent were using illicit drugs.

TABLE 2

TIME ON NALTREXONE (WEEKS)

		High Intervention (N=22)	Low Intervention (N=15)
Total Sample	Mean	8.0	3.6
	Range	1-26	1-12
From Methadone Maintenance (N=18)	Mean	6.5	4.1
	Range	2-18	1-12
From Illicit Opioids (N=19)	Mean	9.3*	2.1
	Range	1-26	1-7

* $p < .05$

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FIGURE 3

NALTREXONE ATTRITION RATES FOR WEEKS 1 to 26
(6 MOS.) FOR HIGH vs. LOW INTERVENTION GROUPS

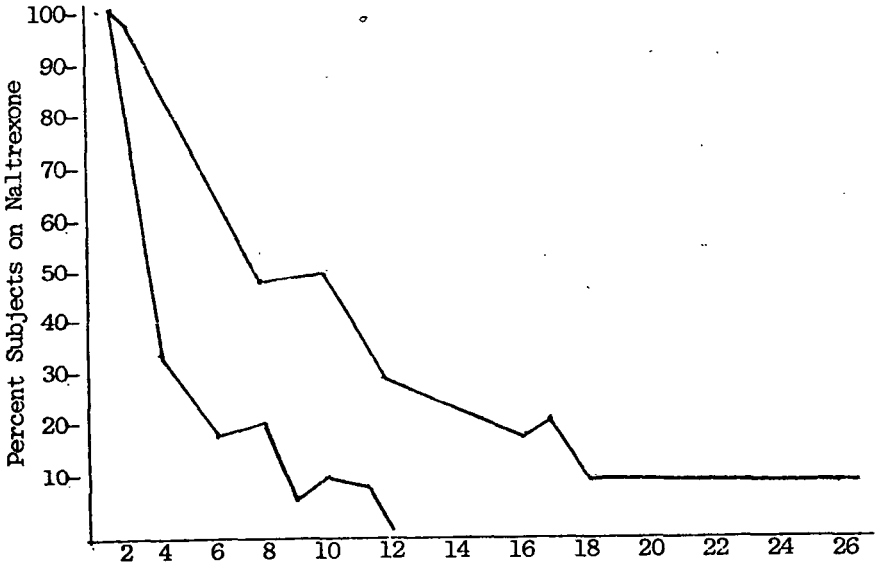
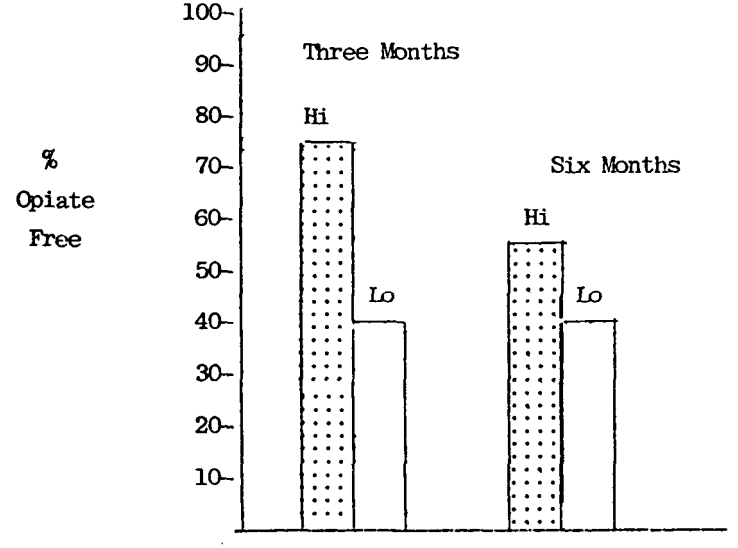


FIGURE 4

FOLLOW-UP AT THREE AND SIX MONTHS AFTER FIRST NALTREXONE DOSE FOR HIGH AND LOW INTERVENTION GROUPS



DISCUSSION

We anticipated numerous problems in controlling the level of staff intervention in a therapeutically oriented clinic that requires frequent visits for medication. Specifically, we expected difficulty in limiting the services provided to low intervention subjects for two reasons: 1) all patients in the study were required to attend the clinic three times per week for medication and therefore would have frequent contact with the clinic staff; and 2) therapists assigned to case managers for low intervention patients would have difficulty in limiting service delivery since this would be contrary to their training and philosophy.

The present study shows that it was possible to control the amount and type of services rendered to patients by the therapists who participated in the study. However, it was very difficult for the majority of nursing and counseling staff not involved in the study to limit contacts with low intervention patients, my of whom received considerable unplanned and unrecorded intervention that my have had a significant impact upon treatment outcome.

The amount of time in Medical/Data Collection contacts was rather high during the early phases of treatment, although there was no difference between the two treatment groups. During these "medical" contacts there was substantial encouragement and emotional support given to the patients which may have obscured differences in detoxification success rates between the high and low intervention groups.

An additional factor which may have reduced outcome differences between the two treatment groups is that three of the six subjects in the low intervention group who were opiate-free at six months follow-up had been receiving regularly scheduled psychotherapy at other facilities.

ACKNOWLEDGEMENTS

This research was supported in part by grant No. R01 DA01555-02 from the National Institute on Drug Abuse. The authors are grateful to Elaine Schuyten-Resnick, C.S.W. and Marlene Fromberg, M.S.W., for assisting with the conduct of the study,

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Type of Pre-Treatment Income and Response to Treatment in Methadone Maintenance

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INTRODUCTION

Among the major goals of psychiatric treatment in general, and drug abuse rehabilitation in particular, is the development of the patient's ability to support himself in a socially desirable manner. Operationally, this means reducing dependence on public assistance and illegal income, while increasing employment earnings. This goal, in particular, may be central to the overall rehabilitation effort and the maintenance of treatment gains in the areas of drug abuse and psychosocial adjustment.

It must be admitted that treatments for drug abuse have had limited success in achieving the goal of patient self-support (Savage and Simpson 1977; Veterans Administration 1979; Sells and Simpson 1976). However, given the variations within the drug-abusing population, it is possible that treatment programs which are only moderately effective with the total population, might be particularly successful (or unsuccessful) with specific subgroups of the population. In this regard, we felt that the amount and sources of patient's pre-treatment income might serve as predictors of post-treatment adjustment in the area of self-support. Specifically, we had noticed three distinctly different sources of income within our patient population: earnings from employment, money from public assistance or other support agencies, and illegal income. We were, therefore, interested in the relationships between these three sources of income within the population and the extent to which these relationships changed following drug abuse treatment.

METHOD

Subjects - Subjects were 165 male narcotic-dependent veterans admitted to the methadone maintenance program of the Drug Dependence Treatment Service (DDTS) at the Philadelphia VA Medical Center. This sample included all patients who were admitted during the period July 1, 1978 to June 30, 1979 and who remained in treatment for at least one month.

Data Collection Instrument - The instrument used to provide both the admission and six-month data was the Addiction Severity Index (ASI) which is described in detail in another article within this volume (Veterans Administration 1979).

Procedure

We initially focused on those questions from the admission ASI which identified the amount and sources of the patient's net income during the 30 days prior to the start of treatment. It should be noted that these responses were self-reports, and while some of the figures were estimates, validity checks were built into the ASI and we have found this self-report data to be generally quite accurate (Ball 1972; McLellan and Druley 1977). An examination of the data suggested that the sources of monthly income could be condensed into three categories: employment, support, and illegal.

Employment income was defined as the net cash value of salaries earned from full or parttime work from either regular or unreported "odd jobs." Unemployment compensation was not included. Eighty-nine patients (54 percent) reported some income from employment at the time of admission.

Support income was defined as the total value of monies derived from public assistance (DPA), Social Security, pension, health benefit plan, and from family or friends. Only cash income was included, thus room and board were not considered in this total. Ninety-five patients (58 percent) reported some income from support sources (generally DPA) at the time of admission.

Illegal income was estimated as the net worth of cash and goods received from criminal activity. The majority of illegal income was derived from burglaries, theft, robbery, or drug sales. Eighty-three patients (50 percent) reported some income from illegal activity.

Twenty-one patients (12 percent) reported income from only one of these sources, 66 (40 percent) reported two sources, and 44 (27 percent) reported three sources of income. The mean income for the total population during the month preceding admission was $510 (S.D.=640) with an average of $230 (S.D.=612) from illegal sources, $206 (S.D.=418) from employment, and $74 (S.D.=216) from social support. However, the population mean and standard deviations for each of these sources indicated considerable population variance in the amount and sources of income, suggesting that the population might be comprised of several distinct subgroups having more homogeneous types of income.

The admission income data indicated that 43 patients had had virtually no income during the month preceding drug treatment, due to hospitalization or incarceration. An inspection of the individual income data on the remaining patients suggested that most subjects received the majority of their monthly income from one of the three major income sources. We therefore attempted to divide the remain-

ing patients based on the source of at least 45 percent of their total monthly income. This division resulted in 30 patients who received at least 45 percent of their monthly income from employment, 42 who received primarily support, and 36 patients who reported primarily illegal income. An additional group of 14 patients comprised a heterogenous group of subjects who did not fit into the prior categories for various reasons. Thus, in the remainder of the paper we will focus upon the main income groups since they presented the clearest income picture and were representative of three basic economic subtypes within the population.

The admission status of each of the three main income groups is shown in table 1 in terms of demographic, background and treatment history measures. Although the groups were rather similar with regard to several of the demographic and educational variables, there were clear differences among them in most of the comparison items. It is important to note that the total monthly incomes within each of the three groups were approximately normally distributed with small standard deviations, thus quite representative of the income patterns of the individuals within each group.

RESULTS

Population Change - The pre-post comparisons (paired t-test) for the three major groups, as well as the total population (N=165) are summarized in table 2. The table presents mean values for each of the major groups on the ASI problem severity ratings, the days of patient-reported problems, and the amounts of the three income sources. The comparisons for the total population are presented in the last columns of table 2, and as can be seen, there were significant reductions in problem severity in the areas of drug abuse ($p < .01$) , employment, and criminality ($p < .05$) . The subjective reports of the patients also showed a significant ($p < .01$) reduction in the average number of days of drug use, from 20 in the month prior to admission to 13 in the month prior to follow-up. Similar reductions in "problem days" are seen in all areas, significantly so in the areas of unemployment and family and social problems. Finally, an examination of the population income figures indicates a considerable increase (57 percent) in the total income from employment.

Changes in Income Groups - The pre-post comparisons for the three major groups in the present study reveal the disparity of posttreatment change within the population. While these three groups were roughly alike in terms of their patterns of pretreatment problem severity, only the Employment and Illegal groups showed evidence of significant improvement by the time of follow-up. Both the Employment and Illegal groups reported significantly fewer days of drug use and unemployment, as well as fewer days of family and social problems. Significantly fewer criminal acts were shown by the Illegal group, and fewer days of psychological problems were reported by the Employment group. The improvement for these groups was most evident in the significant reduction of illegal income with corresponding increases in employment earnings.

The performance of the Support group stands in marked contrast to the results for the other two groups. The patients in the Support group showed little criminal activity or illegal income at either comparison point, but they also showed little evidence of employment or income from earnings. In addition, there were no significant changes shown in the other indicants of psychosocial adjustment. Thus, methadone maintenance was not associated with posttreatment improvement in any area for this group.

DISCUSSION

From a clinical perspective, two points were evident from the data. First, specific improvement in the area of patient self-support was highly related to general improvement in personal and psychosocial adjustment. While it was not possible to determine the causal agent in this relationship, the initial reduction of illicit drug use may have made increased employment and decreased criminality possible. It seems likely, however, that the maintenance of reduced drug use and increased psychosocial adjustment may have relied heavily upon the development of adequate and stable source of employment.

A second point which was clear from the data was that patients' pretreatment source of income was a powerful predictor of treatment benefit. With regard to the actual outcomes of the study groups, the results were somewhat surprising. The exceptional improvement shown by the Illegal group was gratifying considering the reluctance on the part of many programs to accept criminal justice system referrals. The absolute lack of improvement in the Support group stands in direct contrast to the results for the Employment and Illegal groups. We were struck by the stability of the Support group over time, the increase in support income from admission to follow-up, and the general absence of employment or illegal income in the majority of these patients at both admission and follow-up. The subjects in this group may be characterized as the "lethargic" patients who apparently have little involvement with active pursuit of income from either employment or illegal sources. It is important to note that the poor employment record of this group was apparently not due to more physical disability nor to less education and technical training (see table 1). Rather, these data suggest that many of the patients in the Support group may be characterologically dependent upon government sources of income, as well as physically dependent upon opiates. This characterological or institutional dependence may be a major reason why the Support group showed no evidence of improvement in any area. It may be that these patients require a program of intensive vocational and motivational development as an adjunct to existing methadone maintenance. Regardless of the potential reasons for their performance, it seems clear that the program of methadone maintenance and counseling which was associated with significant improvement in the majority of this population was not effective with this particular group of patients. It remains to be seen if these results are generalizable to other drug abuse treatment programs and to nonaddict populations. Nonetheless, the methodology presented here is relevant to the evaluation of drug abuse treatments, and the results may be useful in the clinical management of other rehabilitation programs.

TABLE 1

ADMISSION STATUS OF 165 METHADONE MAINTENANCE PATIENTS

VARIABLE	EMP.	SUPP.	ILLEGAL	TOTAL	SIG
N	30	42	36	165	
MEAN AGE	28	29	28	28	
% BLACK	47	62	48	52	+
YRS. EDUC.	10.5	11	11	11	
MOS. TECH. TRNG.	5	3.5	3	3	
% W/SKILL OR TRADE	68	71	73	70	+
% MARRIED/COHABIT	37	40	38	39	
MEAN # PREVIOUS TREATMENTS					
DRUG	2.5	6.5	3	3.5	+
ALCOHOL	1	2.5	1	1.5	
PSYCH.	.5	1.0	.5	1.0	
% W/PHYSICAL DISABILITY	3	5	3	4	
% GENERALLY EMPL. PAST 3 YRS.	40	7	34	29	*
% ARRESTED MAJOR CRIMES	11	6.5	14	10.5	*
MEAN TOTAL ARRESTS	3	1.5	4	3.5	+
INCOME PREVIOUS MONTH					
EARNINGS	516	58	194	206	
SUPPORT	41	187	71	74	
ILLEGAL	181	41	623	230	
TOTAL	738	286	888	510	

TABLE 2

PRE-POST TREATMENT COMPARISONS

	EMPLOYMENT		SUPPORT		ILLEGAL		TOTAL[1]	
+ = p < .05 * = p < .01	30		42		46		165	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
SEVERITY RATINGS 0-9								
Abuse	6.0	4.0	7.0	6.0	6.0	3.5*	6.6	5.0*
Medical	3.0	3.0	4.0	3.5	3.5	3.0	3.5	3.0
Emp/Sup	3.0	3.0	5.5	5.5	5.0	4.0+	5.5	4.5+
Emp/Sup	5.0	4.5	5.0	4.5	6.0	4.0*	5.5	4.5+
Legal	4.0	2.5*	3.0	2.5	6.5	3.5*	4.0	3.0
Psych	4.5	2.5*	5.5	5.0	3.0	3.0	4.5	3.5
PROBLEM DAYS PAST MONTH								
Used Drugs	23	11*	21	17	24	13*	20	13*
Med. Probs.	4	3	6	4	5	4	5	4
Days Unemp.	15	8+	19	15	14	10+	16	11+
Fam/Soc Probs.	11	8	4	6	13	8*	12	7+
Crime Days	6	3	4	4	11	6*	7	4
Psych Probs.	6	2+	6	6	4	3	6	5
INCOME PAST MONTH								
Earnings	516	631*	58	64	194	501*	206	341*
Support	41	30	187	201	71	44	74	68
Illegal	181	116+	41	440	623	247*	230	112*
TOTAL	738	777+	286	305	888	792+	510	521

'Results for the Jail (N=19), Hospital (N=24), and Other (N=14) group comparisons are presented in the text.

ACKNOWLEDGMENT

Supported by HSR&D Projects 284 and 525 from the Veterans Administration.

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Certain Types of Substance Abuse Patients Do Better in Certain Kinds of Treatments: Evidence for Patient-Program Matching

A. T. McLellan, C. P. O'Brien, L. Luborsky, K. A. Druley, and G. E. Woody

INTRODUCTION

Recently, there have been criticisms of treatment effectiveness in the mental health field, especially the available treatments for the substance abuse disorders of alcoholism and drug addiction (Cummings 1979). The results of several treatment evaluation studies in substance abuse have contributed to this view (Edwards et al. 1977; Armor 1978; Bale et al. 1980). These studies have concluded that while there is evidence that substance abuse treatments are generally more effective than no treatment, there is no indication that different types of treatments produce significantly different outcomes, or that these particular types of treatment are differentially effective with specific types of patients.

The present paper reports evidence of significant differences in outcome among six treatment programs, and evidence for differential effectiveness of these treatment programs with various types of substance abuse patients. This evidence results from a cooperative, Veterans Administration study of substance abuse treatment effectiveness in a population of approximately 1000 male, veteran alcoholics and drug addicts from the Philadelphia region. The design of the study has been described previously (McLellan et al. 1980), and we have shown greater improvement and better outcomes in the treated groups than in a slightly treated control group (McLellan et al. under review). Thus, the purpose of this paper is to examine the issue of patient-program matching and to offer some methodological explanations for the lack of differential treatment effects in previous evaluations.

METHOD

Treatment Programs - The substance abuse treatment network of the Veterans Administration in the Philadelphia area consists of 4 inpatient (2 alcohol, 1 drug, 1 combined) programs at the Coatesville VA Medical Center, plus outpatient alcohol and drug abuse clier at the Philadelphia VA Medical Center. This treatment network has enjoyed cooperative referral arrangements since 1975. Once admitted

to substance abuse treatment at either hospital within the network, patients were assigned to one of the six rehabilitation programs on the basis of their personal requests, the clinical judgment of the admitting staff, administrative considerations such as bed census or patient visit criteria, and simple chance.

Subjects - All male veterans who presented for alcohol or drug abuse treatment at either the Coatesville or Philadelphia VA Medical Centers during 1978 were eligible for the study. There were no significant differences in demographic or background characteristics between patients in the two hospitals, and approximately 90 percent of all subjects were Philadelphia residents. There were no treatment admission criteria other than eligibility for veterans' benefits.

We initially evaluated 1035 male veterans who were admitted to alcohol (N=671) or drug abuse (N=364) rehabilitation programs at the Coatesville or Philadelphia VA Medical Centers during 1978. Since the aims of the study were confined to patients who had been effectively engaged in the treatment process, we did not follow patients who dropped out of treatment prior to 5 inpatient days or 5 outpatient visits. We were able to contact approximately 85 percent of the remaining 879 patients six months after admission to treatment, and complete data were therefore available on 742 subjects (460 alcoholics and 282 drug addicts).

All followup evaluations were done through ASI interviews between an independent research technician and the patient, either in person or over the phone. While much of the data is self-reported, the ASI has built-in validity checks and we have found this self-report data to be reliable and generally accurate (Ball 1972).

PROCEDURE

Developing Appropriate and Reliable Measures of Outcome - We felt it was important to develop general measures of outcome since assessments based solely on single item criteria (e.g., days of drug use) offer meager and inherently unreliable (Nunnally 1967) estimates of posttreatment status. We therefore constructed composite outcome measures based on combinations of objective items from each of the ASI areas. Several of the objective items within each ASI area were intercorrelated to eliminate unrelated items, and the remaining items were standardized, summed, and tested for conjoint reliability using Cronbach's formula (Cronbach and Farby 1970). In this manner seven composite criteria were constructed from sets of the ASI objective items, producing highly reliable (.73 or higher) general measures of outcome in areas which are commonly affected by alcohol and drug abuse treatments.

Assessing the Role of Patient Factors and Treatment Program in Determining Outcome - We were primarily interested in whether some programs had shown better posttreatment outcomes than others, and whether certain "types" of patients appeared to have better outcomes in certain programs. However, we knew that the treatment programs and the patients in them were quite different at the out-

set of treatment, thus it would not be meaningful to compare outcome results directly. We, therefore, required a statistical procedure which would allow us to account for this pretreatment variation and still detect outcome differences among programs and among patient-program combinations. To this end we employed the stepwise multiple regression procedure (Cohen and Cohen 1975).

The multiple regression analysis permitted us to sequentially enter independent (predictor) variables which we considered important in determining outcome as measured by each of our composite scores. For each of these independent variables the regression analysis performed two important functions. First, it tested whether the specific independent variable explained a significant ($p < .01$) proportion of outcome variance. Stated differently, the procedure was able to determine if patients who differed on demographic, admission status or during-treatment variables (e.g., age, race, years drinking, ASI psychological severity score), had significantly different scores on the outcome measure. Secondly, the regression procedure removed that portion of outcome variance accounted for by all of these variables. In this manner, it was possible to adjust (control) for pre-existing differences in demographic and admission status factors before testing for significant effects due to treatment programs and patient-program matches.

Four demographic variables were entered first (Age, Race, Education, Number of Previous Treatments), followed by the pre-treatment ASI severity scores (depicting the admission status of the patients) and then the during-treatment measures of days-in-treatment and type of discharge. Therefore, the criterion measures were adjusted for differences in each of these variables prior to tests for differences among programs and patient-by-program interactions.

RESULTS

Initial Findings for Alcoholics and Drug Addicts Examined Separately - Regression analyses were calculated separately for the alcoholic (N=460) and drug addict (N=282) samples on each of the seven outcome criteria. An examination of the overall results indicated that the majority of variables which were significant ($p < .01$) determinants of outcome were demographic or admission status variables. Disappointingly, there was virtually no evidence of significant patient characteristic-by-treatment program interactions in either sample. In short, these initial findings were quite comparable to results of previous national reports showing no differences in outcome among different treatments or among different patient-program combinations.

However, the results did show a clear and significant ($p < .01$) relationship between the outcome measures and the patients' pretreatment ASI psychological severity score. The correlations between admission psychological severity and the six-month outcome measures were calculated for both the Alcoholic and Drug Addict samples. Significant relations were seen on 5 of the 7 measures for the alcoholics, and on 4 of the 7 criteria for the drug addicts. In every case, greater pretreatment psychological severity was related

to poorer six-month outcome, and this variable alone accounted for an average of 10 percent of the outcome variance.

The strength and pervasiveness of these relationships in the present data suggested the possibility of further dividing the Alcoholic and Drug Addict samples into LOW, MID, and HIGH groups, based upon their pretreatment psychological severity scores, under the assumption that qualitatively different results might appear. Thus the regression analyses were repeated and were calculated separately for each of these six groups.

Interpretation of Regression Analyses - Since seven regression analyses were computed for each of these six groups, there were obviously a large number of individual predictors for specific criteria. In order to present these results in a clear and interpretable fashion, we have summarized the data for all regressions in the two LOW groups in table 1, for the two HIGH groups in table 2 and for the two MID groups in table 3. In these tables the left hand margin indicates the category of independent (predictor) variables and the order in which they were entered into the equations.

Findings for the Six Groups - When the Alcoholic and Drug Addict samples were divided into groups based upon the psychological severity measure, several specific relationships emerged which had been masked in the ungrouped analyses. For example, the regression results for the LOW groups were generally similar to the results for the ungrouped data. That is, greater amounts of treatment were associated with better outcomes, but there were no significant differences in outcome between the different programs, and only a few significant patient-program matches. However, an examination of the outcome results (McLellan et al. under review) indicated that these LOW group patients showed the best posttreatment status and the most significant amount of improvement on virtually all measures. These data lead us to conclude that the LOW severity patients have the best treatment prognosis generally, and appear to improve significantly in any of the treatment programs to which they are assigned. The admission characteristics of these patients and the type of improvement shown are suggestive of the small group of alcoholic patients described in the Rand Study (Armor et al. 1978) who were able to return to "social drinking" following treatment. It may be that non-abstinent goals are possible for some members of this more intact group of patients. From a practical perspective we have recommended that the majority of these LOW severity patients be treated in an outpatient setting since this is the most economical, and seemingly equally effective alternative. Despite this general conclusion, the data indicate (consistent with our clinical experience) that even with the generally favorable prognosis for this group, patients with significant family and/or employment problems should be treated in an inpatient setting.

The results of our analyses in the HIGH groups also showed few significant differences in outcome among programs and no significant patient-program matches. However, unlike the LOW groups the HIGH severity patients did not show better outcome with more treatment.

We have previously reported (Gottheil et al. 1980) on this growing proportion of psychiatrically ill substance abusers, and have discussed the special problems involved in treating them, within either psychiatric or substance abuse programs. The present data, our earlier reports, and our clinical experience indicate that none of the programs currently available within our treatment network are effective with these individuals. Interestingly, although treatment outcome could not realistically be called satisfactory, the Methadone Maintenance Program appeared to have the most positive impact on the HIGH severity drug patients, possibly due to the regulatory and weak anti-psychotic effects of the methadone (McLellan et al. 1979). In view of these results! we have recommended the formation of a special, inpatient psychiatric-substance abuse ward, staffed and run by psychiatrists and psychiatric personnel. It is hoped that by focusing primarily upon the psychiatric aspects of these individuals' addiction syndromes, it will be possible to control their substance abuse.

Once the HIGH and LOW groups (which comprised approximately 40 percent of the total population) were separated from the remaining (MID) population it was possible to discern significant differences in outcome associated with specific treatments, and especially associated with specific patient-program matches. For example, MID patients (alcoholics and drug addicts) with more severe family and/or employment problems had poorer outcomes in outpatient treatment. These findings are consistent with our clinical experience and suggest that while severe alcohol or drug use, and even medical or legal problems, may be dealt with effectively in an outpatient setting, family and employment problems appear to be clear contraindications for outpatient treatment. Finally, two of the inpatient alcohol abuse treatment programs showed evidence of poorer outcomes with clients having more serious legal problems. We have suggested that these clients be transferred to the Combined Treatment Program or (in some cases) the Alcohol Outpatient Program which did not show poorer outcome with these patients.

Clinical Implications - The present data, and other reports (McLellan et al. 1980; McLellan et al. this volume) indicate the importance of making independent pretreatment assessments of patient status in several areas commonly affected by addiction. These addiction-related problem severity measures were the most significant predictors of outcome in all groups. The fact that patients with greater pretreatment psychological severity showed the poorest outcome is not surprising. What is remarkable is that alcohol and drug abuse severity were not generally important in predicting outcome. In fact, pretreatment psychological severity was a better predictor of posttreatment drinking than pretreatment drinking. This finding in particular suggests why previous predictive studies which have used brief data collection instruments concentrating on demographic and substance abuse variables have not demonstrated meaningful outcome prediction.

Finally, the demonstration of significant differences in outcome

as a function of interactions between patient factors and treatment programs suggests that different forms of substance abuse treatment, like other medical treatments, have specific as well as general effects. Further, the data illustrate how the specific effects of the treatment programs may combine with the particular treatment needs of the patient to produce favorable outcomes, as well as clear contraindications. We were gratified that the patient, treatment, and patient-by-treatment factors which were statistically significant in the analyses also made conceptual and clinical sense. These factors which were statistically significant predictors of outcome in the present study will be utilized as determinants of treatment assignment in the next stage of our project (McLellan et al. 1980). Thus, we will be able to determine if these factors can be of practical value in producing improved treatment effectiveness for the six-program treatment network.

ACKNOWLEDGMENT

This work was supported by HSR&D Project #284 from the Veterans Administration. The technical assistance of Mr. Frank Erdlen, Mr. David LaPorte, Mr. Richard Parente, and Mrs. Diane Hery, and the cooperation and support of the Coatesville VA Medical Center are gratefully acknowledged.

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Table 1

OUTCOME PREDICTORS IN LOW SEVERITY PATIENTS

Type of Variable	ALCOHOLICS N=102		DRUG ADDICTS N=68	
	Variable	R [1]	Variable	R [1]
DEMOGRAPHIC	# Prior Trts.	.32	--------	
ADMISSION SEVERITY	Medical Severity Employ. Severity	.33 .28	Drug Use Sev. Employ Sev.	.30 .30
DURING TREATMENT	Days in Trt.	-.20	Days in Trt.	-.28
TREATMENT PROGRAM	--------		--------	
INTERACTIONS	Legal Sev. X FIDD	.28	Emp. Sev X MM	.28
MEAN OUTCOME VARIANCE EXPLAINED		34%		32%

Table 2

OUTCOME PREDICTORS IN HIGH SEVERITY PATIENTS

Type of Variable	ALCOHOLICS N=82		DRUG ADDICTS N=53	
	Variable	R [1]	Variable	R [1]
DEMOGRAPHIC	Age	.30	--------	
ADMISSION SEVERITY	--------		Drug Use Sev.	-.26
DURING TREATMENT	--------		--------	
TREATMENT PROGRAM	COMB AOP	.36 .37	COMB	.44
INTERACTIONS	--------		--------	
MEAN OUTCOME VARIANCE EXPLAINED		48%		54%

[1] Mean correlation between predictor and the seven outcome criteria

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TABLE 3

OUTCOME PREDICTORS IN PATIENTS WITH MID-LEVEL PSYCHOLOGICAL SEVERITY

Type of Variable	ALCOHOLICS N=276		DRUG ADDICTS N=161	
	Variable	R[1]	Variable	R[1]
DEMOGRAPHIC	Age	.38	Race	.37
	# Prior Trts.	.34	Age	-.27
ADMISSION SEVERITY	Family Sev.	.28	Employ. Sev.	.36
	Legal Sev.	.26		
DURING TREATMENT	Days in Trt.	-.38	Days in Trt.	-.35
	Type Disch.	-.26	Type Disch.	-.27
TREATMENT PROGRAM	FIDD	.25	COMB	.33
INTERACTIONS	Legal Sev. X FIDD	.31	Fam. Sev. X MM	.37
	Emp. Sev. X AOP	.30	Emp. Sev. X MM	.34
	Legal Sev. X ATU	.28	Med. Sev. X DAR	.30
	Age X COMB	.25	Drug Sev. X COMB	.28
	Fam. Sev. X AOP	.24		
	Fam. Sev. X ATU	.24		
MEAN OUTCOME VARIANCE EXPLAINED		44%		48%

[1]Mean correlation between predictor and the seven outcome criteria

A Quantitative Evaluation of Fetal Growth Failure in a Drug-Abusing Population

R. J. Wapner, J. Fitzsimmons, R. D. Ross, M. E. Rudrauff, A. B. Kurtz, and L. P. Finnegan

An association between maternal drug abuse during pregnancy and low birth weight infants is known. A significant proportion of these low birth weight infants are felt to be small for gestational age (SGA). The growth pattern and possible etiologies of growth failure in these fetuses have not been well documented.

In order to study fetal growth, ultrasonic scans were performed on 99 patients of The Family Center Program at Jefferson between 1/1/78 and 12/31/79. Biparietal diameters (BPD), head circumferences, abdominal circumferences, and total intrauterine volumes (TIUV) were measured. At delivery, weight, height, head circusference and gestational age by Dubowitz score of each newborn was recorded. Infants whose weight fell below the tenth percentile for gestational age were considered to be SGA. By this criterion, 13 infants had growth retardation.

Of the scans performed on infants who at birth were determined to be adequate for gestational age, all showed TIUV's and BPD's in the normal range. However, 11 of the 13 SGA infants had BPD's more than two stardard deviations below the mean, and 11 of 13 had total intrauterine volumes in the abnormal range: i.e. more than one standard deviation below mean. These findings were evident as early as mid-second trimester, and were shown to persist through the third trimester in patients having serial scans. The ratio of head to body circumferences approaches one in both the sonographic and postpartum measurements in these SGA infants. Both the early evidence by sonography of altered fetal growth, and the symmetric nature of the deficit indicate an early onset type of growth retardation. This is in contrast to the more common late onset, asymmetric form seen typically with "supply-line" defects secondary to placental insufficiency.

The incidence of growth retardation in the subgroup of patients

abusing pentazocine was statistically higher ($p < .01$) than that expected in the total population. Mothers using methadone did not demonstrate a significantly increased incidence of SGA infants. Pentazocine-abusing mothers constituted only 9.1 percent of Family Center patients, while their infants represented 53.8 percent of growth retarded infants in the study.

The early onset, symmetric form of growth retardation found in these patients is typical of a direct, teratogenic drug effect on the early developing fetus. This effect is most marked in patients abusing pentazocine.

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Alcohol Tolerance Development in Humans: Tests of the Learning Hypothesis

R. E. Mann and M. Vogel-Sprott

Tolerance to alcohol may be defined as a reduction in response to a given dose of alcohol after repeated administrations. A great deal of research has been devoted to the study of this phenomenon (1), but studies of tolerance development in humans who are not alcoholic have been few, perhaps because such studies were thought to expose participants to the risk of developing dependence on alcohol. However, recent studies suggest that tolerance development can be studied safely in human social drinkers (2,3). As well, similarities between learning and some forms of tolerance to drugs have been described (4,5,6,7,8). This paper reports two studies designed to test the hypothesis that tolerance to alcohol in human social drinkers may be subject to the laws of instrumental learning.

EXPERIMENT 1

Animal research has shown that the development of tolerance on behavioral measures is often dependent upon the reinforcement contingencies which maintain those behaviors. Specifically, tolerance seems most likely to occur when the initial effects of a drug act to reduce the amount of reinforcement received by the organism, a principle first described by Schuster and his coworkers (4). Recent human studies suggest a parallel between animal and human research in this respect; tolerance developed on a paper and pencil coding task where intrinsic reinforcement contingencies were operating (2,3), but not on a pursuit rotor task where no reinforcement was available (3,9). The first experiment tested the prediction, derived from the learning hypothesis, that tolerance to the effects of alcohol on pursuit rotor performance would develop when reinforcement for nonimpaired performance was provided.

Eight male undergraduate volunteers were randomly assigned to either an alcohol (A) or placebo (P) group (n=4 per group). After predrug training (36 50-sec. trials on the Pursuit Rotor over two days) the subjects attended four drinking sessions, separated by a mean of 3.3 days. In each drinking session group A subjects received alcohol (.88 ml 96 percent alc/Kg body weight) while group P subjects received a placebo beverage. Pre and postdrug pursuit

rotor tests, alcohol administration, and blood alcohol content (bac) measures followed a standardized schedule in each drinking session (3,10).

The pursuit rotor task used was basically identical to that used in the alcohol studies in which no tolerance development was observed (3,9). Thus, subjects tracked a light source moving in a square pattern with a photosensitive hand-held stylus. The speed of the rotor was 30 r.p.m. and a test on the task consisted of two 50-second trials separated by a 30-second intertrial interval. The subject's score on a test was his average time on target during the two 50-second trials. This study modified the task by introducing reinforcement for performance. The reinforcement provided consisted of augmented auditory feedback, posttrial performance information, and monetary reinforcement. Further details on reinforcement procedures can be found in (10). Blood alcohol levels were obtained with a Omicron Intoxilyzer.

The drug-free performance of subjects in groups A and P did not differ significantly during the practice period. Their initial drug-free tests, which preceded alcohol tests on each session, also did not differ. Thus the drug-free performance of the two groups was essentially equal throughout the entire experiment. Examination of bac readings from group A revealed a typical bac curve, and no differences over sessions were observed.

The differences between a subject's drug-free score on a session and each of his five subsequent alcohol tests in that session were calculated to provide measures of change in performance. A negative difference thus obtained indicated that performance under alcohol was poorer, or impaired, relative to the subject's nondrug state. Variance analysis of the pursuit rotor difference scores (2 groups X 4 sessions X 5 trials) revealed a significant groups X sessions interaction ($F=3.989$, $df=3/18$, $p<.05$), presented in table 1. On the first session the two groups were clearly different, with group

TABLE 1

Mean Change (in Seconds) from Daily Drug-Free Baseline - Experiment 1

	Drinking Sessions			
Groups	1	2	3	4
Group P	1.28	-.97	1.83	-.13
Group A	-2.52*	-2.26	2.16	.42

*for $p<.05$ on a two-tailed t-test, an absolute difference of 2.45 between groups is required (11).

A showing a strong performance deficit. However, by the final session the groups did not differ, due to the fact that group A no longer displayed impairment.

EXPERIMENT 2

The results of the first experiment support the learning hypothesis, in that tolerance developed to the impairing effects of alcohol with the appropriate reinforcement conditions. The results of other studies show no tolerance on this task (3,9); the suggestion is that the difference in tolerance development between the first experiment and other studies was due to the differences in reinforcement contingencies. However, this comparison is between separate experiments, and interpretation must be tentative. For this reason, an additional study was designed to replicate the first study and include a group of alcohol subjects not given reinforcement. This second study also served to test an additional prediction concerning the loss of tolerance. Specifically, if the acquisition of tolerance observed in this paradigm is an instrumental learned response, then withdrawal of reinforcement from subjects showing tolerance should result in extinction, or a return of impaired performance.

Twelve male undergraduate volunteers were randomly assigned to one of three groups. Two alcohol groups and one placebo group were employed. One alcohol group (n=4) received reinforcement (AR), the second alcohol group (n=4) did not receive reinforcement (ANR) and the third group was a placebo group (n=4) which received reinforcement (P). The subjects attended two predrug practice sessions followed by six drinking sessions. The drinking sessions were a mean of 4.01 days apart. The pursuit rotor and intoxilyzer employed in this study were identical to those employed in the first experiment.

The procedures for reinforcement administration to the AR and P groups in the two practice sessions and the first four drinking sessions were identical to those for the A and P groups in the first experiment. In the final two drinking sessions, the extinction hypothesis was tested by withholding all reinforcement contingencies from these groups. Thus, the auditory feedback was withdrawn, no posttrial performance information was given, and subjects could not earn any more money for nonimpaired performance. Subjects in the ANR group did not receive any of the reinforcement conditions at any point in the study. Testing schedules, the dose of alcohol or placebo, and drinking schedules in all sessions were identical to those used in the first study.

The drug-free baseline measures of performance from the drinking sessions showed no differences between groups or over sessions, indicating that drug-free performance remained stable and comparable throughout the experiment. Bac measures showed a typical bac curve, consistent over sessions with no differences between AR and ANR groups.

Each of the five postdrug measures of performance in each session for each subject was expressed as a difference from that subject's baseline score in that session. Variance analysis of these data (3 groups X 6 sessions X 5 trials) revealed a significant inter-

action of groups and sessions (F=3.777, df=10/45, p<.01), presented in table 2. On the first two sessions, the two alcohol groups

TABLE 2

Mean Change (in Seconds) from Daily Drug-Free Baseline-Experiment 2

	Drinking Sessions					
Groups	1	2	3.	4	5	6
Group P	1.08a	.45a	.20a	.53a	-2.43	1.20a
Group AR	-2.28b	-2.54b	-.89a	-.33a	-4.06	-5.53ab
Group ANR	-2.52b	-2.30b	-3.86b	-3.62b	-3.22	-3.31b

For p<.05 on a two-tailed t-test, an absolute difference between groups of 2.06 is required (11).

a - Differs from Group ANR, p<.05
b - Differs from Group P, p<.05

showed significant impairment relative to the placebo group, and did not differ from each other. On sessions three and four, however, the reinforced alcohol group showed tolerance, in that it did not differ from the placebo group, while the nonreinforced alcohol group remained significantly impaired relative to the placebo and reinforced alcohol group. Finally, on sessions five and six when reinforcement was withdrawn, the reinforced alcohol group showed a decline in performance which resulted in significant impairment relative to both of the other groups on session six.

DISCUSSION

The results of both studies agree with the predictions based upon an instrumental learning hypothesis of alcohol tolerance. Tolerance to the impairing effects of alcohol developed when appropriate reinforcement contingencies were in place, did not occur when reinforcement contingencies were not present, and disappeared (showed extinction) when reinforcement contingencies were withdrawn from tolerant subjects. These results are not predicted by metabolic, biochemical, or physiological theories of tolerance which emphasize chronic administration, and the results occurred under conditions which should minimize the effects of nonlearning variables (i.e., low doses, separation of testing sessions). The conclusion suggested by these findings is that there exists at least one form of tolerance to alcohol which is a learned response, and which might complement other forms of tolerance.

The learning hypothesis of tolerance is useful in that it generates some very specific predictions about tolerance acquisition, the amount of tolerance displayed in a situation, and the loss of tolerance. For example, although it appears that tolerance can be acquired very quickly under appropriate environmental conditions, tolerance may also disappear by means of a very simple change in

those conditions. Thus, further testing of the learning hypothesis may have some important applied and forensic implications, as well as being of theoretical interest.

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ACKNOWLEDGEMENTS

This work was supported by a National Health Student Fellowship to R.E.M. and by grants from the Non-Medical Use of Drugs Directorate to M.V.-S.

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The New Mixed Agonist-Antagonist Analgesics, Nalbuphine and Butorphanol, vs. Pentazocine: Relapse and Substitution in Morphine-Addict Rats

G. F. Steinfels, G. A. Young, and N. Khazan

INTRODUCTION

The therapeutic efficacy of the narcotic drugs in the treatment of cough, pain, and diarrhea is unsurpassed by drugs of other pharmacological classes. While these effects have been known and utilized over many centuries, the euphoric and other psychological properties of narcotics have made them prime candidates for abuse. This has prompted researchers over the past several decades to search for compounds that possess similar therapeutic efficacies to that of a narcotic such as morphine but devoid of the side effects and abuse potentials. One general class of narcotic compounds that has resulted from this intensive search is the mixed agonist-antagonist analgesics. Three of these compounds, being pentazocine, nalbuphine, and butorphanol, were of special interest to us in our ongoing studies on narcotics since each is currently available for therapeutic use as a potent analgesic.

We speculated that tendencies of morphine postaddict rats to relapse to self-administration of such compounds might provide ditional information for the assessment of degree of abuse potential for at least two reasons. First, the morphine postaddict rats would have a history of drug self-administration but would be neither tolerant to nor physically dependent on a narcotic. Thus, no precipitation of withdrawal would occur if these rats were given the opportunity to relapse to the self-administrationof these mixed agonist-antagonists. This is in contrast to a direct substitution procedure in which a mixed agonist-antagonist would presumably precipitate abstinence in morphine-dependent rats. Second, one would not have to contend with problems of training the postaddict rats to self-administer the drugs, because each rat would already have established a history of self-administration. Thus, any possible reinforcing properties of a mixed agonist-antagonist

would be disclosed in a morphine postaddict rat. Therefore, the tendencies of morphine postaddict rats to relapse to the self-administration of pentazocine, nalbuphine, and butorphanol were comparatively studied.

METHODS

Adult female Sprague-Dawley rats were prepared with chronic EEG and temporalis EMG electrodes (Khazan et al. 1967, Khazan 1975). Stainless steel screws which served as bipolar cortical electrodes were implanted over the frontal (2 mm anterior and 2 mm lateral to bregma) and the ipsilateral parietal cortex (3 mm posterior and 2 mm lateral to bregma). For drug injections, a silicone rubber cannula was implanted into the right external jugular vein (Weeks 1962). Each rat was maintained in an individual cage that was equipped with a response lever, a swivel cable connector for EEG and EMS recordings, and a feed-through cannula for drug administration. EEG and EMG activities were recordedon a Grass model 7D polygraph . The EEG was filtered to pass frequencies between land 30 Hz.

Forty rats were first made tolerant to and physically dependent on morphine by a series of electronically-controlled automatic iv injections. During the first day, the rats received 1.25 mg/kg/hr of morphine sulfate. The dose was increased to 2.5, 5.0, 10.0 and 20.0 mg/kg/hr on successive days. The rats were then trained to lever press on a fixed ratio (FR) schedule of reinforcement to receive morphine (10 mg/kg/injection over 3 sec). A FR of one lever press was initially required per injection, which was gradually increased to FR-20. After one week of stabilized responding for morphine, the rats were divided into two main groups. In one of these groups each rat was removed from the experimental cage and allowed to withdraw from morphine in the home cage for two weeks. Each rat was then returned to the experimental cage and given the opportunity to reestablish self-administration of morphine (10 mg/kg/injection), pentazocine (1 mg/kg/injection), nalbuphine (5 mg/kg/injection), butorphanol (0.5 mg/kg/injections), or 0.9% saline. In the second of morphine-dependent rats pentazocine, nalbuphine, butorphanol at the above doses, or naloxone (0.5 mg/kg/injection) or mathadone (2 mg/kg/injection) was directly substituted for morphine.

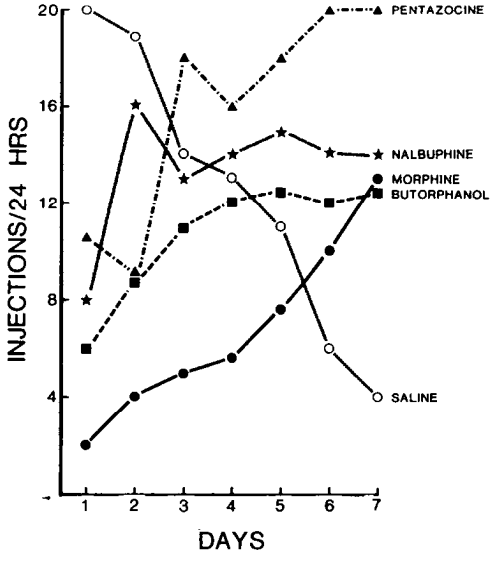
The study of REM sleep distributions during self-maintained dependence on narcotics in the rat has elucidated similarities and differences in pharmacodynamic profiles among narcotics (Moreton et al. 1976, Young et al. 1979a). Also, the relative degree of REM sleep suppression has proven to be a reliable indicator of severity of withdrawal from narcotics (Young et al. 1977, 1979b), andbehavioral states of sleep, REM sleep, and wakefulness were identified by the corresponding changes in gross behavior and in EEG and EMG recordings (Khazan et al. 1967, Khazan and Weeks 1968, Moreton et al. 1976). Thus, REM sleep times per 24 hours and REM sleep distributions were also assessed in the present study. Occurrences of lever presses and injections were recorded on the

polygraph as well as on an Esterline-Angus event recorder.

RESULTS

When morphine postaddict rats were given the opportunity to relapse to the self-administration of morphine, the man daily number of self-injections gradually increased over days and was stabilized within a week (Figure 1). The patterns of mean daily number of self-injections during relapse to the self-administration of pentazocine, butorphanol, and nalbuphine were similar to that for morphine. In contrast, when morphine postaddict rats self-administered saline, the mean total number of self-injections was very high on the first day and steadily decreased over the seven days of relapse studied.

FIGURE 1

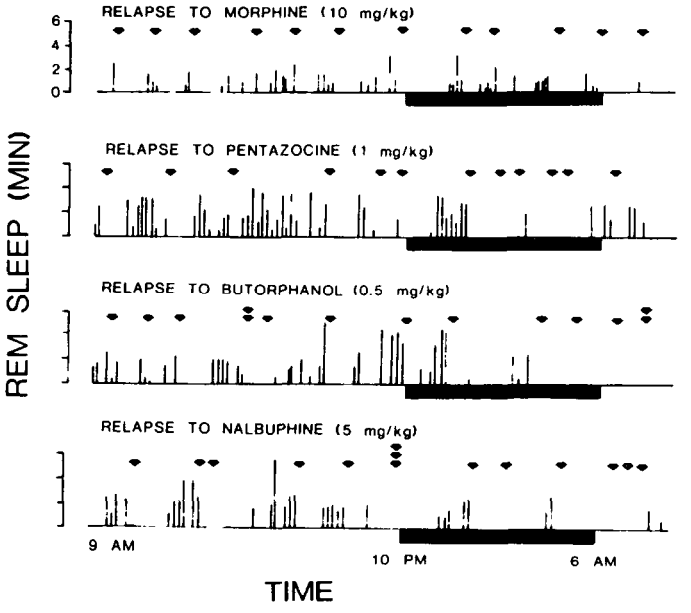


Mean daily number of self-injections are shown over seven days of relapse to the self-administration of morphine, pentuzocine, butorphanol, nalbuphine, and saline.

Upon stabilization of drug self-administration (i.e., on the seventh day of relapse in a moqhine postaddict rat relapsing to morphine self-administration) the characteristic pattern of self-injections and distribution of REM sleep episodes seen earlier (Khazan and Weeks 1968) is presented in the top row of Figure 2. This individual rat, for example, took single injections of morphine (10 mg/kg/injection) at intervals of about 2 hours. Each morphine self-injection usually suppressed occurrences of REM

sleep for 30 min or more, after which they reappeared and persisted until immediately before each subsequent morphine self-injection. Furthermore, Figure 2 also sham that patterns of self-injections and distribution of REM sleep episodes on the seventh day of relapse to self-administration of pentazocine, butorphanol, and nalbuphine in morphine postaddict rats were similar to those during relapse to morphine . Single and, occasionally, multiple self-injections were relatively equally spaced, and REN sleep occurrences were also suppressed for about 30 min or more after self-injections.

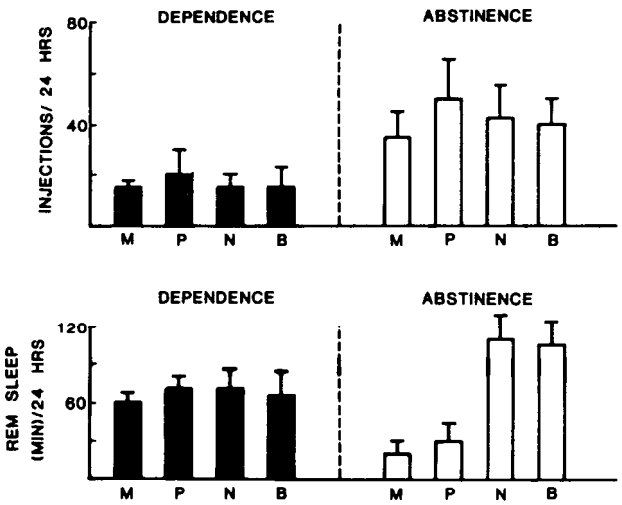
FIGURE 2



REM sleep distributions for individual rats during the seventh day of relapse. Data are shown during relapse to the self-administration of morphine, pentazocine, butorphanol, and nalbuphine. Self-injections are indicated by the filled arrows.

Grouped data during the seventh day of relapse to narcotic self-administration in morphine postaddict rats and during the first day of subsequent saline substitution are shown in Figure 3. During the seventh day of self-administration mean daily numbers of self-injections were similar at the dose levels used for morphine, pentazocine, butaphanol, and nalbuphine. During the first day of sub-Sequent saline substitution mean daily numbers of self-injections increased for all four drugs. Furthemore, during relapse the mean daily REM sleep time in min was on the lower edge of control values for all four drugs. However, during the first day of subsequent saline substitution the mean total amount of REM sleep was suppressed with morphine and pentazocine but not with butorphanol and nalbuphine.

FIGURE 3



Grouped data during the seventh day of relapse to narcotic self-administration in morphine postaddict rats and during the first day of subsequent saline substitution. Mean daily numbers ± s.e.m. of self-injections and mean daily times in min of REM sleep are shown for morphine, pentazocine, buturphanol, and nalbuphine.

During stabilized self-maintained dependence on morphine the substitution of methadone (2 mg/kg/injection) for morphine supported dependence. When pentazocine, butorphanol, nalbuphine, or naloxone was substituted for morphine, occurrences of REM sleep were severely supressed . As expected, the rats also exhibited signs of abstinence such as diarrhea, "wet-dog" shakes, and abdominal stretching. The effects of naloxone substitutionwere similar to those of the three mixed agonist-antagonists.

DISCUSSION

Morphine postaddict rats relapsed to the self-administration of morphine, pantazocine, butorphanol, and nalbuphine. Relapse to morphine self-administration in postaddict rats has been previously demonstrated (Weeks and Collins 1968, Moreton et al. 1975, Young et al. 1975). Several characteristics of relapse to self-administration of pentazocine, butorphanol, and nalbuphine in the present studywere similar to those with morphine. All of these drugs were self-administered periodically and self-injections of each usually suppressed occurrences of REM sleep for 30 min or more. When saline was substituted for each of these drugs, self-injections

greatly increased in number. All of the above observations suggest that the drug-seeking by the rat was eminent for the four narcotics studied.

When saline was substituted for the respective narcotic, occurrences of REM sleep were severely suppressedduring abstinence from morphine and pentazocine. However, REM sleep suppression was not observed during abstinence from butorphanol and nalbuphine. Furthermore, abstinence from morphine and pentazocine was associated with behavioral symtoms such as diarrhea, "wet-dog" shakes, and irritability, while abstinence from butorphanol and nalbuphine was not. These findings suggest that there was considerable physical dependence in rats dependent on morphine and pentazocine, but relatively little physical dependence on butorphanol and nalbuphine. Thus, the above data also seem to differntiate between drugs which induce both psychological and physical dependence such as morphine and pentazocine, and drugs which produce a similar psychological dependence with apparently minimal physical dependence such as butorphanol and nalbuphine. While differences in degree of physical dependence were disclosed between morphine and pentazocine on the one hand and butorphanol and nalbuphine on the other hand, drug-seeking behavior for all four compounds was found to be similar.

Finally, pentazocine, butorphanol, and nalbuphine did not substitute for morphine during self-maintained dependence, since abstinence was precipitated in all three cases. since these mixed agonist-antagonists did not support dependence in the "substitution" procedure it was assumed that each drug possesses a relatively low abuse potential. However, for all three mixed agonist-antagonists in morphine postaddict rats, relapse to self-administration was established in a manner similar to morphine. Therefore, our findings showed that butorphanol and nalbuphine demonstrated addiction liability in the relapsing morphine postaddict rat. However-, this addiction liability appeared to consist of more psychological dependence than physical dependence in contrast to the addiction produced by morphine.

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ACKNOWLEDGEMENTS

Supported by NIDA Grant 01050. Thanks are due to Endo Laboratories, Inc., for providing nalbuphine hydrochloride and to Bristol Laboratories for providing butorphanol tartrate.

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Effects of Route of Administration on Methadone Disposition in the Rat

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The long-acting narcotic, dl-methadone, has been used since 1964 for the chronic treatment of patients addicted to heroin (Dole et al. 1966). Clinical experience with over 85,000 patients maintained on daily oral doses of methadone has shown that this method of treatment is effective. Despite the effectiveness of orally administered methadone in the treatment of addiction, the analgesic properties of methadone have been shown to be reduced when the drug is administered by the oral, rather than a parenteral route of administration (Beaver et al. 1967). Studies have shown that when. methadone is administered orally on a chronic basis in the rat, measurable plasma levels of drug are achieved with apparent terminal half-life similar to that observed following subcutaneous administration (Kreek 1979). Also, it has been shown that estrogen and alcohol both interact with methadone following oral administration in ways that significantly alter overall methadone disposition (Kreek et al. 1980; Wendell et al. 1979). Yet, experimentally demonstable tolerance and dependence could not be developed in rats given orally administered doses of methadone, nor could withdrawal be induced through the administration of the narcotic antagonist, naloxone (Harris et al. 1978).

This study was undertaken to compare the distribution of methadone plus metabolites (measured as total radioactivity from methadone), when the drug was administered by the oral, subcutaneous and intravenous routes. This information complements previous methadone disposition studies (Adler and Eisenbrandt 1949; Elliot et al. 1949; Way et al. 1949; Misra et al. 1973). It was hoped that information from these studies could provide insight into the kinetics and, thus, possibly action of methadone in the rat model following each route of administration as well as to delineate to what extent orally administered methadone should be active in the rat.

METHODS AND MATERIALS

Male Sprague-Bawley rats weighing 150 to 200 g were obtained from Charles River Breeder (Wilmington, MA). The animals received Purina Lab Chow and water ad libitmn and were kept in a temperature

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controlled room With a conventional day-night lighting schedule. The rats were divided into two study groups, receiving either acute or chronic treatment. An acute treatment group received a single tracer dose of ^{14}C radiolabeled dl-methadone HCl (1.3 mg free base; 3.125 µCi) by the oral, subcutaneous or intravenous route of administration. The ^{14}C dl-methadone, labeled in the 2-carbon position, was obtained from California Bionuclear Corporation (Sun Valley, CA) and demostrated to be radiochemically pure (>95 percent) by thin layer chromatography with zonal scanning. A second, chronic treatment group was formed. One-third of this group received chronic pretreatment which consisted of 2 weeks of oral administration of dl-methadone HCl (1.15 mg free base initially increased to 1.3 mg free base after week one) to achieve a final dose of 5 mg/kg rat weight/day. This Was followed by the administration of a single oral dose of ^{14}C dl-methadone. The remaining two-thirds of the chronic treatment group received pretreatment with dl-methadone administered by the subcutaneous route in the same dosages as given to animals treated by the oral route. After two weeks of pretreatment, half of these rats received a single tracer dose of methadone administered by the subcutaneous route and the other half by an intravenous injection into the tail vein of each animal. All rats in the chronic treatment group received ^{14}C dl-methadone HCl in the same dosage as rats in the acute treatment group (1.3 mg free base; 3.125 µCi).

Three to five animals Were studied at each time point by each route of administration following both acute and chronic methadone administration. Rats Were kept in metabolic cages for collection of urine until time of sacrifice 30 minutes to 24 hours after the single tracer dose administration. Animals were sacrificed by exsaguination through the inferior vena cava following light ether anesthesia. Half of the total volume of blood Was centrifuged to obtain plasma; and the other half was analyzed as whole blood. Organs were removed, Weighed and frozen in physiological saline solution.

Each organ was homogenized using a Polytron PCU-2-110(Brinkmann Instrmnents, Westbury, NY). Two-hundred fifty µl aliquots of each homogenate were taken in triplicate, dried at 37° C in combustible capsules and radioactivity was recovered by oxidation using a TriCarb 306 Sample Oxidizer(Packard Instrument Co., Downers Grove, IL). Radioactivity Was measured by liquid scintillation counting (Packard TriCarb Model C2425), and appropriate quench corrections were made.

Thin layer chromatography with zonal scanning using methods previously described from this laboratory was carried out to determine relative amounts of unchanged methadone and metabolites in liver and brain at the one-hour time point following both oral and intravenous tracer dose administration in the chronic treatment group (Kreek et al. 1978).

RESULTS

The results of this study may be divided into two parts. The concentrations and total amount of radioactivity from methadone, thus including both methadone and its metabolites in various organs and tissues, may be compared with respect to the route of administration, and the relative amounts of drug in different organs within a given treatment group may be assessed.

Methadone and metabolites, measured as total radioactivity in tissue homogenates, were found to be present in all organs studied at all time points between 30 minutes and 24 hours. As shown in Table 1, the route of administration had only a small effect on the total radioactivity from methadone recovered over the calculated 23-hour (1 hour to 24 hours after tracer dose administration) period in the liver and whole blood of rats in the acute treatment group. Oral

Table 1

Total amounts of methadone and its metabolites in organ during 24-hour interval following drug administration (ng equivalent/organ/24 hours)[a]

		Acute			Chronic		
		po	sc	iv	po	sc	iv
Whole Blood	Ng Eq[b]	7420	8060	9050	6271	7876	7799
	Ratio-	0.819	0.891	1	0.804	1.010	1
Liver	Ng Eq	100500	101360	92410	121143	65768	69370
	Ratio	1.088	1.097	1	1.746	0.948	1
Brain	Ng Eq	290	970	770	212	718	684
	Ratio	0.372	1.253	1	0.310	1.050	1
Lung	Ng Eq	1510	11910	10850	1553	9035	8092
	Ratio	0.139	1.098	1	0.192	1.117	1
Kidney	Ng Eq	2830	10700	9150	2196	6869	7026
	Ratio	0.309	1.169	1	0.313	0.978	1
Spleen	Ng Eq	290	2560	2710	340	2441	2818
	Ratio	0.106	0.942	1	0.121	0.866	1
Testes	Ng Eq	580	7070	5440	531	5389	5434
	Ratio	0.107	1.299	1	0.098	0.992	1
Adrenals	Ng Eq	60	270	200	53	167	179
	Ratio	0.277	1.322	1	0.296	0.933	1

[a] Time points: Chronic = 60m, 90m, 3h, 6h, 24h;
Acute = 60m, 3h, 6h, 24h

[b] po ratio = po/iv
sc ratio = sc/iv
iv set to equal 1.0

administration of tracer dose did result in reduced radioactivity recovered in other organs. Brain, kidney and adrenals of rats receiving an oral dose contain approximately 30 percent of the radioactivity found in these organs in rats receiving an intravenous dose. Lung, kidney and spleen of rats receiving an acute oral dose contain approximately 10 percent of the radioactivity found in these organs in rats receiving an intravenous dose. Similar results are found for rats receiving chronic methadone pretreatment with one exception; livers of rats receiving chronic Oral pretreatment contain substantially more radioactivity from methadone than livers of rats receiving chronic pretreatment by either parenteral route.

Figures 1-3 show total content of methadone and metabolites (measured as radioactivity and expressed as nanogram equivalents of methadone/organ) at specific time points following radiolabeled dose administration by the oral, subcutaneous or intravenous route of administration. Naive rats received a single radiolabeled dose of methadone (5 mg free base/kg body weight). Each point represents mean value (± SEM) for all animals studied at each time point (number of animals, 3-5 at each time point). These figures show that the reduced amounts of radioactivity from methadone that were observed in the organs and tissues of rats receiving an oral radiolabeled dose (Table 1) resulted from reduced amounts in these organs at the early time points. At 24 hours following radiolabeled dose administration, route of administration does not significantly affect amount of radioactivity recovered in any organ except the testes in the acute treatment group.

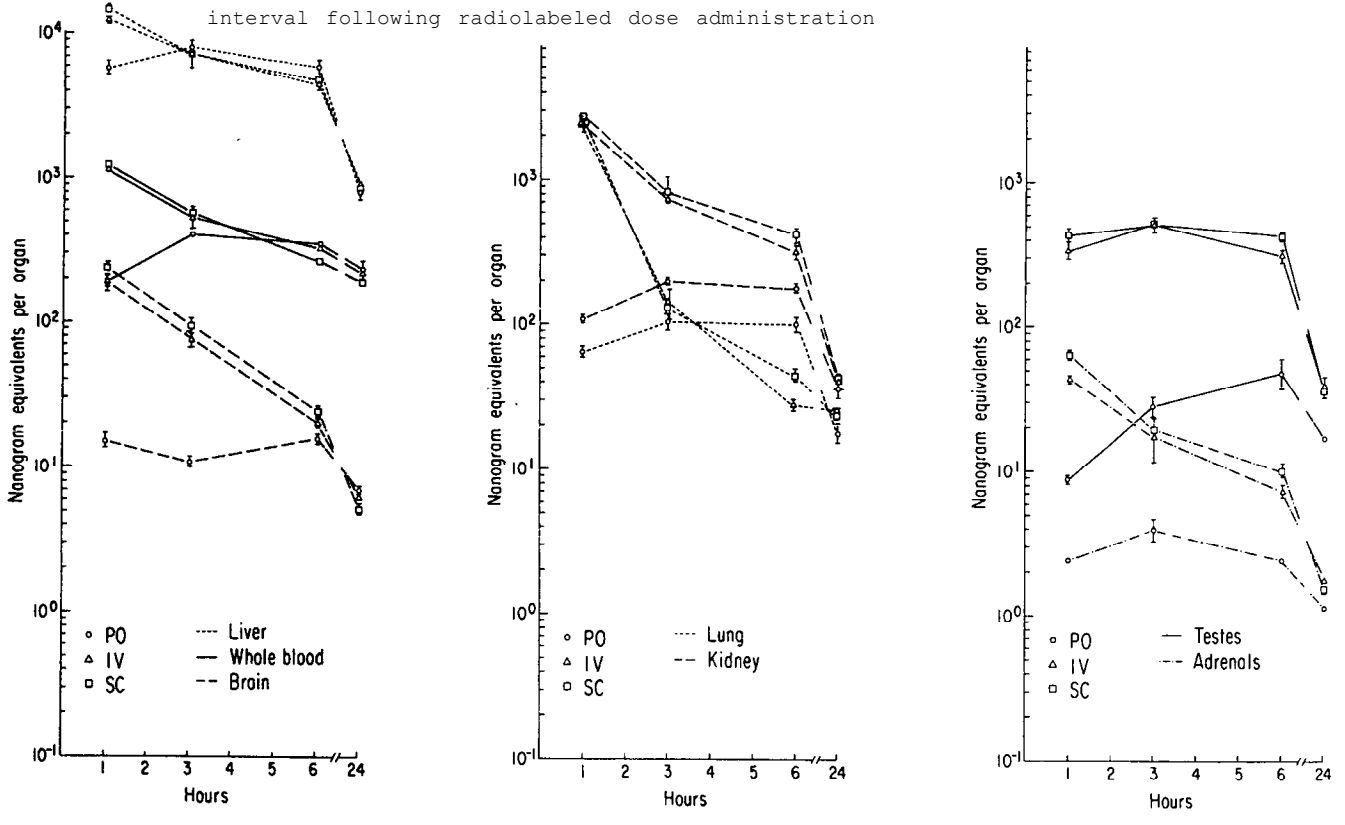
The mean terminal half-life (3-24 hours) of total radioactivity was calculated for all of the, organs and tissues studied in the chronic treatment group. Table 2 shows that mean terminal half-life for all organs of rats receiving an oral radiolabeled dose is longer than the mean terminal half-life for organs of rats receiving a radiolabeled dose by either parenteral route. However, the difference in overall organ disappearance rates for total radioactivity from methadone is due to very slow disappearance of compounds (or persistence of compounds) in the brain, whole blood, adrenals and testes.

Table 2

Mean apparent terminal half-life (3-24 hours) of total radioactivity including methadone and metabolites in chronically treated rats

	Oral	Subcutaneous	Intravenous
All organs	14.2 hours (± 2.2 SEM)	7.7 hours (± 1.7 SEM)	7.0 hours (±1.0 SEM)
Liver, Lung Kidney, Spleen	7.6 hours (± 0.3 SEM)	5.72 hours (± 1.14 SEM)	8.30 hours (± 1.69 SEM)
Whole Blood, Brain, Testes, Adrenals	19.5 hours (± 1.5 SEM)	9.73 hours (± 3.02 SEM)	5.66 hours (± 1.01 SEM)

Figures 1-3. Total amounts of methadone and metabolites in organs over a 24-hour interval following radiolabeled dose administration



DISCUSSION

The results of this study expand upon and reinforce previous studies of the effect of route of administration on methadone disposition in the rat. Specifically, this study protocol allows the direct comparison of data from rats receiving an oral, subcutaneous or an intravenous dose of methadone and also analysis of the effect of route of administration on the distribution of methadone and metabolites to organs not previously studied in this manner.

Methadone administered to the rat clearly is extensively metabolized, but also stored and concentrated in major organs. Although the levels of methadone and metabolites observed in many organs are sharply reduced When the drug is administered by way of the oral route, high levels of total radioactivity from methadone are observed in the liver and blood following oral administration which are similar to levels observed in rats receiving treatment by the parenteral routes. In rats receiving a single radiolabeled dose of dl-methadane following tracer dose administration, livers were shown to contain 87 percent of the amount of unchanged methadone found in rats receiving methadone by the intravenous mute. Thus, route of administration ties little difference on either the amounts of unchanged methadone or metabolized methadone found in the liver. However, in the chronic treatment group, at the one-hour time point following tracer dose administration, brains of rats receiving methadone by the oral route contain only 3 percent of the amount of unchanged methadone found in brain of rats receiving methadone by the intravenous mute. These highly significant differences may explain the differences in acute analgesia observed both in rats and in man when methadone is given by the oral as opposed to the intravenous route of administration.

The data from this study, combined with previous data from this laboratory concerning long-tern Persistence of dl-methadone in tissues (Harte et al. 1976), show that a measurable mount of unchanged methadone could be present in the brain for at least 24 hours. This amount of active narcotic may be sufficient to develop a degree of tolerance in the rat, albeit insufficient to produce symptoms of tolerance and physical dependence measurable by currently available, well-tested and validated methods. The estimated total binding capacity of specific opiate receptors in the brain is very low. Thus, even small amounts of active narcotic available to critical receptor sites may bind to a physiologically, if not pharmacologically, significant percentage of sites (Snyder et al. 1974).

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ACKNOWLEDGMENTS

This study was supported by NIDA Grant DA-01138 and Grant Number 112926 from the New York State Division of Substance Abuse Services. Dr. Kreek is the recipient of an HEW-ADAMHA-NIDA Research Scientist Award (DA-00049).

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Androgenic-Like Effects of Morphine in the Male Rat

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INTRODUCTION

Narcotics produce dose-dependent decreases in serum luteinizing hormone (LH) levels in the male and female of several species (Bruni et al. 1977; Cicero et al. 1977a; 1977b; Mirin et al. 1976; Muraki et al. 1977; Pang et al. 1977;). This effect appears to be due to a direct action of the narcotics on the hypothalamus, presumably by an inhibition of the release of L&releasing hormone (LH-RH) (Rotsztejn et al. 1978); furthermore, it has been established that the LH-depleting effects of the narcotics are mediated by specific opiate receptors (Cicero 1977; Cicero et al. 1977a; 1977b; Pang et al. 1977; Rotsztejn et al. 1978).

The existence of opiate receptors in the hypothalamus mediating the effects of narcotics on the hypothalamic-pituitary-LH axis suggests that there may be endogenous opioids which normally play an inhibitory role with respect to the secretion of LH. Support for this hypothesis has been provided by several groups of investigators who have shown that narcotic antagonists, such as naloxone, significantly increase serum LH levels after their administration to male and female rodents and humans (Blank et al. 1979; Bruni et al. 1977; Cicero et al. 1979; 1980; Meites et al. 1979; Mendelson et al. 1979). Moreover, we have reported that naloxone blocks testosterone's negative feedback control of the hypothalamic-pituitary-LH axis in the male rat (Cicero et al. 1979). These results, coupled with the observation that certain endogenously occurring opioid peptides (e.g., methionine-enkephalin) also depresss serum LH levels (Bruni et al. 1977; Meites et al. 1979), give strong support to the hypothesis that opioid-containing neural elements are intimately involved in the neuroendocrine control of reproductive endocrinology.

If, as suggested by the preceding studies, an endogenous opioid is involved in regulating activity in the hypothalamic-pituitary-LH axis, and in mediating the negative feedback control of this axis exerted by testosterone, then it should follow that morphine and related narcotics should mimic the acute and chronic effects of testosterone on the hypothalamic-pituitary-LH axis. However, it would

be expected that this androgen-like activity should be confined to the hypothalamus since narcotics do not apparently exert any important effects on the pituitary (Cicero et al. 1977a; 1977b; Pang et al. 1977), whereas testosterone has activity at both sites (Bogdanove et al. 1975; Damassa et al. 1976). The present studies were carried out to examine these possibilities.

METHODS

Testosterone-Like Effects of Morphine——Acute Studies

To determine whether morphine, like testosterone, acutely depressed serum LH levels in the castrated male rat, Sprague-Dawley-derived male rats were injected either with testosterone (500 µg/rat) or morphine (5 mg/kg) 48 hours after castration. They were then killed at intervals after drug administration and LH levels were determined as described elsewhere (Niswender et al. 1969). On the basis of these time-course studies, the interval at which peak depressions in LH occurred (24 hours for testosterone and 30 minutes for morphine) was used to construct dose-response curves for each test drug.

Testosterone-Like Effects of Morphine——Chronic Studies

To examine whether testosterone would reverse the long-term postcastrational changes in hypothalamic LH-RH content, LH concentrations in the pituitary and serum LH levels, groups of rats were castrated or shamoperated and immediately thereafter were injected, subcutaneously, with testosterone (500 µg/rat) or sesame seed oil; these injections were continued for 14 days, and groups of rats were killed at 3, 7, 10 and 14 days. Blood was collected from the decapitated carcasses for determining serum LH levels (see above). In addition, the anterior lobe of the pituitary and the brains were obtained. The pituitaries were homogenized in phosphosaline (pH=7.4) and LH levels were determined by radioimmunoassay (Niswender et al. 1969). Hypothalami were dissected from the brains at -20°C and were homogenized in 2 ml 0.2N acetic:absolute ethanol (1:1, V/V). They were then centrifuged, and LH-RH content was determined in dilutions of the supernatant fluids by a double-antibody radioimmuoassay described elsewhere (Nett et al. 1973).

To examine whether morphine, like testosterone, would reverse the changes induced by castration, groups of rats were castrated or sham-operated and were then implanted with morphine pellets, containing 75 mg morphine base, or placebo pellets, containing lactose, on a regimen described elsewhere (Cicero et al. 1977b). This procedure results in relatively constant serum and brain levels of norphine for an extended period (Hipps et al. 1976). Rats were killed 3, 7 and 10 days later. Serum and pituitary LH levels and hypothalamic-LH-RH content were determined as described above. A 10-day treatment interval was used in these studies, as opposed to the 14-day treatment interval in the case of the testosterone-replacement experiments, to avoid the possible development of tolerance to morphine which develops 13 to 17 days after treatment on this regimen (Cicero et al. 1977b).

RESULTS

Acute Testosterone-Like Effects of Morphine

Single injections of testosterone (500 µg/rat) in the 48-hour castrated animal produced a time-dependent drop in serum LH with the maximum level of depression occurring 24 hours after the injection. Moreover, as shown in table 1, there was an excellent dose-response relationship between the dose of testosterone injected and reductions in serum LH 24 hours after its injection. Morphine (5 mg/kg) also acutely depressed serum LH in the 48-hour castrate. LH levels were significantly depressed within 10 minutes after the injection of the narcotic, and the lowest level of depression (approximately 65 percent with respect to controls) occurred 30 minutes after the injection. Thereafter, LH levels slowly returned to control values. These time intervals correspond quite closely to peak brain and serum morphine levels (Hipps et al. 1976). The dose-effect curve for morphine-induced depressions in serum LH is also shown in table 1. There was an excellent dose-response relationship with essentially linear decreases in LH up to a dose of 4.0 mg/kg when LH levels were reduced to approximately 1/3 of control levels. Higher doses of morphine produced no further decrease in serum LH levels.

Table 1

The effects of testosterone and morphine on serum LH levels in the castrated (48 hr) male rat. Values are means (±SEM) of 8 animals in each group. *p<.05 when compared to control.

	Serum LH (ng/ml)		
Dose (ug/rat)	Testosterone	Dose (mg/kg)	Morphine
Control	765 (±85)	Control	646 (±37)
40	680 (±72)	0.5	505 (±41)*
80	675 (±68)	1.0	475 (±18)*
160	619 (±80)*	2.5	346 (±21)*
320	425 (±46)*	4.0	250 (±26)*
640	155 (±26)*	5.0	218 (± 7)*
1000	148 (±28)*	10.0	220 (±11)*

Testosterone and Morphine Reversal of Postcastrational changes in LH and LH-RH in Serum, Pituitary and Hypothalamus

Following castration in the male rat, serum LH levels rise 10 to 20-fold within 24 hours and remain elevated at this level for approximately 5 days (Badger et al. 1978). Between days 5 to 10 a doubling of LH levels occurs which then persists for weeks or months. This "two-stage" effect of castration is also reflected in pituitary LH and hypothalamic-LH-FH content. During stage 1 (days 1-5), there is little change in pituitary LH or LH-RH in the hypothalamus. During stage 2 (>5 days) there is a substantial increase in pituitary LH levels (2 to 3-fold) and a corresponding decrease (approximately 75 percent) in hypothalamic LH-RH. We found that daily injections of testosterone reversed all of the changes occurring during stages

1 and 2 of castration (data not shown). The effects of morphine and testosterone on the postcastrational changes in hypothalamic LH-RH content are shown in table 2. As can be seen, morphine was just as effective as testosterone in preventing the fall in hypothalamic-LH-RH content which occurred during the second stage of castration. Morphine also suppressed the postcastrational increase in serum LH during stage 1 but was relatively ineffective in stage 2 (data not shown). Moreover, morphine did not reverse the increase in pituitary LH observed during the second stage of castration (data not shown). Thus, testosterone reversed all of the postcastrational changes occurring in the hypothalamus, pituitary and blood whereas morphine selectively reversed only those changes occurring in the hypothalamus.

Table 2

The effects of testosterone and morphine on hypothalamic LH-RH levels (ng/hypothalamus) in castrated or sham-operated male rats. Values are means (±SEM) of 8 to 10 animals in each group. *p<.05 when compared to sham.

	Days			
	3	7	10	14
Sham	1.90 (±.15)	1.98 (±.22)	2.10 (±.46)	2.05 (±.25)
Castrate	1.86 (±.17)	1.05* (±.11)	0.76* (±.09)	0.53* (±.08)
Castrate+Testosterone	2.05 (±.15)	2.52 (±.20)	2.16 (±.25)	2.42 (±.31)
Castrate+Morphine	2.08 (±.26)	2.15 (±.18)	2.32 (±.56)	--

DISCUSSION

The results of previous studies have indicated that endogenous opioid peptides participate in regulating activity in the hypothalamic-pituitary-LH axis and participate in testosterone's negative feedback control of this axis (Blank et al. 1979; Bruni et al. 1977; Cicero et al. 1979; 1980; Meites et al. 1979; Mendelson et al. 1970; Mirin et al. 1976). More recent studies (Cicero et al. 1979; 1980) have further indicated that an opioid-containing cell represents a bridge between the effects of testosterone on the hypothalamus and the ultimate inhibition of LH-RH containing cells. Whether this opioid-containing system is the final link, impinging directly upon LH-RH containing neurons, or is simply part of a complex neural chain is at present unknown.

If the assumption outlined above is correct, then it would follow that opioids should mimic the effects of testosterone in the castrated animal. Our results indicate that acute morphine administration depresses serum LH in the short-term castrated male rat (48 hours) to the same extent as testosterone. As a second prediction derived from the hypothesis that opioid-containing cells serve as a neuronal pathway mediating testosterone's effects, it would also be expected

that morphine should reverse the long-term testosterone-dependent postcastrational changes in the hypothalamic-pituitary-LH axis. However, one would expect distinct differences between the two compounds. Specifically, since morphine exerts only hypothalamic effects within the hypothalamic-pituitary-LH axis (Cicero 1977; Cicero et al. 1977a; 1977b; Pang et al. 1977; Rotsztejn et al. 1978), and testosterone exerts effects at both the hypothalamic and pituitary level (Bogdanove et al. 1975; Damassa et al. 1976), it would be predieted that morphine should reverse only those postcastrational changes in this axis which are in some way mediated by alterations in activity at the level of the hypothalamus. In the present studies we found that morphine completely prevented the marked reduction in hypothalamic-LH-RH occurring during stage 2 of castration. Hence, it appears that morphine exerts rather potent androgen-like effects on the hypothalamus. In contrast to these observations, however, morphine was not capable of suppressing the postcastrational changes in pituitary LH content and blocked increases in serum LH only during the initial phases of castration. Indeed, during stage 2 of castration morphine appeared to exacerbate the effects of castration on both pituitary LH content and serum LH levels. These observations are thus consistent with the interpretation that narcotics exert purely central effects on the hypothalamic-pituitary-LH axis, whereas testosterone exerts effects at both the hypothalamus and pituitary to reverse the changes occurring during stages 1 and 2 of castration.

In summary, the present results further support the concept that endogenous opioids play au important role in the regulation of the hypothalamic-pituitary-LH axis and mediate testosterone's negative feedback control of this axis. Moreover, our results suggest, in agreement with predictions derived from this hypothesis, that morphine exerts androgen-like effects in the hypothalamus.

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ACKNOWLEDGMENTS

This research was supported in part by grant DA-00259 from the National Institute on Drug Abuse. Dr. Cicero is also a recipient of Research Scientist Development Award, AA-70180. Ms. Carol E. Wilcox is deceased.

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Opiate Inhibition of Sheep Erythrocyte Binding to T Lymphocytes: Reversal by Naloxone and Cyclic Nucleotides

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The abuse of street opiates causes both pathological and cellular changes, the etiologies of which are obscure. Spiera et al. (1974) reported an increase in rheumatoid factor activity titre in heroin addicts which disappeared after a year in methadone treatment. This same group (Brown et al. 1974) also found abnormalities in the humoral and cellular immune systems in addicts which included hypergammaglobulinemia and an impaired mitogenic response to phytohemagglutin, pokeweed mitogen and concanavalin A. At the genetic level, Falek and Hollingsworth (1980) found a significant increase in chromosome aberrations in heroin addicts which returned to normal levels after a year in methadone treatment. The etiology of this increase has been inferred from the finding that leukocytes from heroin addicts exhibit a severely reduced capacity to repair DNA damage (Madden et al. 1979). This reduction in DNA repair should predict for the addict both an increase in carcinogenesis and in birth defects. In fact, Sadeghi et al. (1978) have reported a 4-fold increase in bladder cancer in opium addicts, and up to a 20-fold increase in opium addicts who also smoked tobacco while Wapner et al. (this volume) have described a fetal heroin syndrome in children of addicts and former addicts. The cellular mechanisms by which opiate abuse produces these alterations are at present obscure.

Several recent investigators have hypothesized that many tissues outside the neuronal system have opiate receptors which alter the particular functions of those tissues. Wybran et al. (1979) demonstrated an *in vitro* reduction in active T lymphocytes caused by morphine, met-enkephalin, and dextromoramide but not by levomoramide, and that this T cell reduction could be reversed by naloxone. Lopker et al. (1980) reported naloxone-reversible binding of dihydromorphine to phagocytic leukocytes, while

Hazum et al. (1979) showed that lymphocytes bind β-endorphin at a site not inhibited by enkephalins or naloxone. We now report that both chronic and acute opiate use produce cell-mediated immunological changes in vivo including a persistent depression in the percent of total T lymphocytes, and that these changes can be reversed by (-)-naloxone or cyclic nucleotides in vitro.

METHODS

Peripheral venous blood was collected in heparinized tubes from control subjects, street opiate addicts entering therapy programs, and coronary care unit patients receiving intravenous narcotics for relief of chest pain. Each subject completed an informed consent document and a medical history form. Lymphocytes were collected over Ficoll-Paque, washed twice, diluted into GIBCO RPMI 1640 - 50% Fetal Calf Serum and counted. Total T lymphocyte frequencies were determined by the sheep erythrocyte rosette technique using overnight incubation at 4°C (Palmer et al., 1978). B lymphocytes were enumerated by binding of Bio-rad fluorescein-labeled rabbit antibody specific for human IgA, IgG, and IgM (Palmer et al., 1978). Null lymphocytes were described as those lymphocytes which were neither T nor B; and, therefore, % Null = 100 - (%T + %B).

RESULTS

Among 44 street addicts and 28 control subjects from the Atlanta and Chicago areas, white blood cell counts and % B lymphocytes did not vary between any of the groups tested (WBC: addict - 7320, control - 7360; %B cell: addict - 16.3%, control - 17.7%). The percentage of T lymphocytes, however, was significantly lower in the addicts than in the controls; 26% vs 69%, respectively (see Figure 1). Conversely, the addicts had increased Null lymphocytes relative to the controls; 57% vs 13%, respectively. Thus, opiate addicts have decreased ability to form rosettes from sheep cell erythrocytes, thereby reducing T cell counts and increasing Null cell counts. We hypothesize that the opiate blocks the sheep erythrocyte binding site on the T lymphocytes.

The suppression of T cell characteristics by long-term opiate use persists for a significant period of time during detoxification. In a program at McLean Hospital, two addicts were studied longitudinally for 40 days through a protocol of drug-free detoxification, heroin administration, and a final detoxification which included administration of naltrexone. After an initial 20 days of drug-free detoxification, these patients demonstrated a significant depression of % T lymphocytes, no effect on % B lymphocytes, and a significant increase in null cells (Figure 2). Five other addicts (X), also tested at 21 days, showed the same pattern of T cell depression. Administration of 7-14mg heroin, 3 times daily for one week, caused an additional T cell reduction which continued even after withdrawal from the opiate. Thus, the T lymphocyte depression was a persistent effect which could

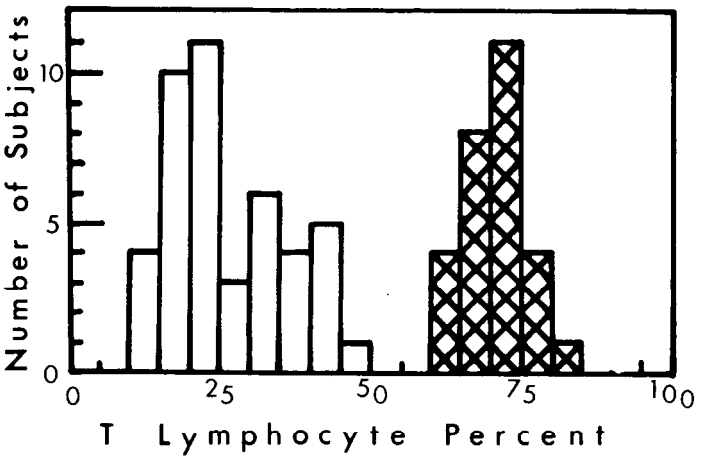

Figure 1. Histogram of T Lymphocyte % in 44 street opiate addicts and 28 control subjects. Lymphocytes from addicts (☐) or controls (☒) were incubated overnight with sheep erythrocytes in RPMI-1640 + 50% Fetal Calf Serum at 4°. 100 cells from replicate cultures were scored for rosette formation.

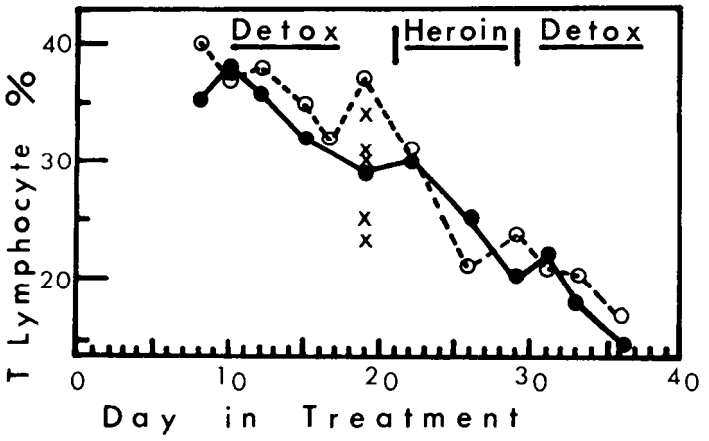

Figure 2. Effect of detoxification and heroin administration on T lymphocyte %. Two addicts (—●— and —○—) were followed longitudinally during alternating periods of drug-free detoxification and heroin administration. Five other addicts (X) were also tested after 20 days of detoxification.

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be measured beyond the time when the drug itself could be detected in the addict.

The T lymphocyte depression can also be found in patients receiving an acute dose of opiate prescribed for the relief of pain. A patient, given 10mg morphine followed by 25mg demerol 24 hr later, showed a typical pattern of T cell depression within 24 hr of the first opiate dose (Figure 3). The depression persisted for about a week, before the % T cells returned to normal levels. These data, and samples from a number of other subjects, suggest that sheep erythrocyte binding suppression is not rapid as would be expected if simple opiate-receptor interactions directly caused the effect. Rather, the suppression required a number of hours for maximal effect, suggesting a more indirect mechanism possibly involving membrane rearrangement as, for example, is the case in phytohemagglutin stimulation of lymphocyte cell division (Kiefer et al. 1980). In fact, Sharma et al. (1977) have reported similar long-term phenomena in opiate stimulation of neuroblastoma in which more than 12 hrs are required before increased adenylate cyclase is realized. Thus, T cell depression can be produced by an acute dose of opiate, but only after a delay of 12 hrs.

The depression of T lymphocyte % caused by either acute or chronic use of opiates can be reversed in vitro by (-)-naloxone, an opiate antagonist, and by cyclic nucleotides (Figure 4). Lymphocytes from patients who received either a single dose in vivo of morphine or demerol were incubated in vitro for 1 hr at 25°C with either 10^{-6}M naloxone, 10^{-4}M adenosine-3':5'-cyclic phosphate (cAMP), 10^{-4}M dibutyryl cAMP (dBcAMP) or buffer alone. Treatment with these compounds reversed the opiate-induced T cell depression (Figure 4), by converting null cells to T cells.

SUMMARY

Acute or chronic use of opiates causes a decrease in T lymphocyte percent as measured by the sheep erythrocyte rosette assay. The effect in chronic addicts persists for at least three weeks after cessation of use, while in acute users the effect reverses more rapidly. Both naloxone and cyclic adenylate nucleotides can reverse the T cell depression supporting the hypothesis that T lymphocytes have membrane opiate receptors analogous to those on neuronal cells. It is tempting to speculate that the T lymphocyte depression caused by opiate use indicates an impairment in lymphocyte function and immune competence which would explain many reported physiological deficiencies found in addicts. The cyclic nucleotide results, for example, suggest that opiates interfere with the regulation of cyclic nucleotides in the lymphocytes, as they do in neuronal tissue. Many authors (Parker, 1979) have described the activation of lymphocyte functions by cyclic nucleotides so that impairment at this level should have major consequences for lymphocyte function. Until specific experiments to quantitate cyclic nucleotide levels and immune competence have

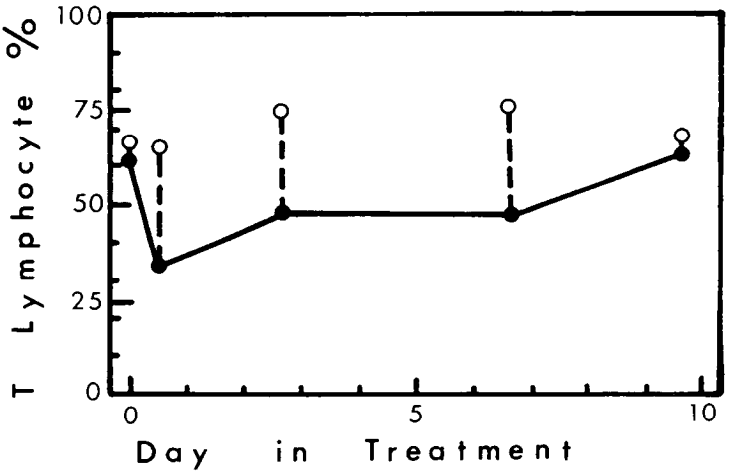

Figure 3. Longitudinal effect of acute morphine administration on T lymphocyte %. A patient received 10mg morphine intravenously for the relief of chest pain. Blood samples were drawn pre-injection (0 time) and longitudinally post-injection. The % T lymphocytes was determined either directly (—●—) or after a 1-hr incubation with 10^{-6}M naloxone at 24°C (—○—).

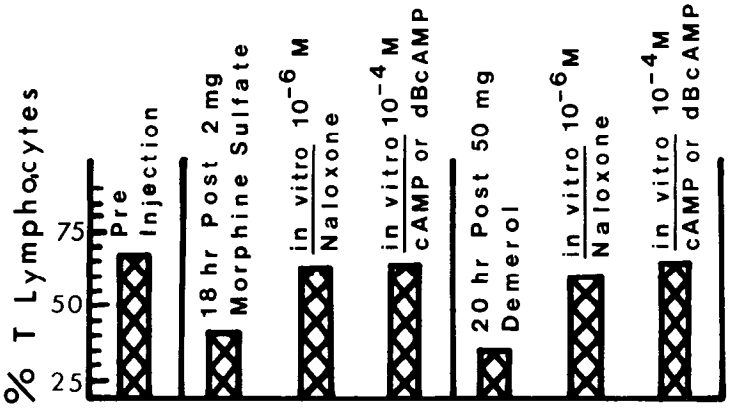

Figure 4. Effect of naloxone or cyclic nucleotides on the T cell depression caused by a single dose of morphine or demerol. Two patients were studied pre-injection and 18-20 hr post-morphine, or demerol, injection. The T cell % was determined with and without a 1-hr incubation at 24°C with either 10^{-6}M naloxone, or 10^{-4}M cAMP or dBcAMP. The pre-injection samples were unaffected by incubation with naloxone or cyclic nucleotides (not shown).

been completed, however, it is not known whether the blocking of sheep erythrocyte binding sites by the opiates affects lymphocyte function. Li et al. (1980) have separated β-endorphin binding activity from analgesic potency in neuronal tissue and it is not clear which lymphocytic activities, if any, correlate with either opiate binding and/or loss of E rosette formation. The fact that both chronic and acute opiate paradigms produce comparable T cell depressions makes the answer a marked necessity considering the widespread medicinal use of opiates.

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ACKNOWLEDGEMENT

This research is supported by NIDA Grant #DA 01451.

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Intravenous Clonidine Self-Administration by Rhesus Monkeys

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Clonidine has recently been reported to provide dramatic relief of withdrawal signs and symptoms in human opiate addicts (Gold et al., 1978, 1980.) Aceto et al. (1979) found that clonidine partially substituted for morphine in morphine-dependent monkeys. With these findings in mind, and considering the possibility of increasing availability of clonidine to the drug abuse population, we have evaluated the ability of clonidine to support intravenous self-administration in rhesus monkeys. Under conditions of limited or unlimited access, clonidine maintained self-administration above saline levels in both drug-experienced and drug-naive animals. In addition, continuous unlimited access to clonidine led to high levels of intake as well as the appearance of abstinence symptoms shortly after abrupt withdrawal of the drug. These symptoms were reversible by clonidine administration and were not precipitated by naloxone.

METHODS

The subjects were 6 male rhesus monkeys. Each monkey was housed in an individual self-administration cubicle and fitted with a stainless steel tubular harness and connecting arm. Under pentobarbital anesthesia the animals were prepared with venous catheters. The catheter exited through the skin on the back and connected through the harness and arm to an infusion pump.

Four monkeys were allowed to self-administer cocaine (30µg/kg/injection) each day for a 2 h experimental session. Ten responses on a lever were required for a 10 sec injection. When daily cocaine self-administration was stable, saline or one of several doses of clonidine (0.3-100µg/kg/injection) was substituted for cocaine for 6 consecutive sessions. Rates of self-administration for the last 3 sessions of clonidine availability were compared to responding during the corresponding sessions of access to saline. The effects of several doses of clonidine were replicated in two monkeys.

Two monkeys have been tested to date under conditions of unlimited access. Monkey #3018 was drug naive while #3147 had been used in other self-administration experiments. Experimental sessions were 23 h long. Beginning at 3:00 p.m. each day, two red lights were illuminated over each of two levers. Each left lever press resulted in a 1 ml injection of the drug or saline vehicle solution. During injections the left lever lights changed from red to white. Responses on the right lever produced the same stimulus change over the right lever but no injection resulted. At 2:00 p.m. the subsequent day the session was terminated, the data recorded, the equipment checked, the cages cleaned, and the total food intake over the preceding 23-hour period determined. After an initial 7 days of access to saline, several unit doses of clonidine were tested for access periods that ranged from 10-30 days. During periods of access to saline that also followed clonidine availability, animals were observed every 4 h and rated using a withdrawal symptoms checklist. In addition, one hour prior to the end of session 86, naloxone (0.1 mg/kg) was administered i.v. to both animals and the effects were recorded. At the same time point during sessions 132, 133 and 134, saline or a naloxone challenge dose of 0.1 or 0.3 mg/kg was administered i.v. in a random fashion and with observer blind to treatment.

RESULTS

The data for limited access are summarized in table 1. Under baseline conditions cocaine maintained stable responding above the range of saline values in all animals. There was, however, considerable variability between subjects in cocaine intake per session, with mean values ranging between 56 and 114 injections per session. Responding for cocaine was relatively evenly distributed over the session with slightly greater than 50% of the injections taken in the first half of the session. In contrast, when saline was substituted for cocaine, low rates of responding (<10 injections/session)were usually observed by sessions 4-6. In addition, responding for saline occurred principally in the first part of the session with more than 75% of the total injections taken in the first half of the session.

TABLE 1

Intravenous Clonidine Self-Administration in Rhesus Monkeys Under Conditions of Limited Access

Clonidine Dose	Injections Per Session		Total Intake (µg/kg/ session)		No. Self-Administered/
(µg/kg/inj)	Mean	Range	Mean	Range	No. Tested*
Saline	6.3	0-23	--	--	--
0.1	19.3	14-29	1.9	1.4-2.9	1/1
0.3	15.2	3-40	4.6	0.9-12	1/3
1.0	12.1	1-32	12.1	1.0-32	3/5
3.0	11.9	1-38	35.6	3-114	3/5
10	18.1	3-77	181.0	30-770	3/6
30	7.0	0-28	210.0	0-840	1/4
100	19.5	9-34	1950.0	900-3400	1/2

*Number of tests where clonidine range did not overlap with saline range. Where number tested >4: 1 or 2 animals were tested twice.

When clonidine was substituted for cocaine, responding above the range of saline levels was observed at least at one dose in all animals. Dose-response curves were somewhat flattened, usually with less than 30 injections/session taken at any dose at any time, and typically of the inverted "U" shape usually described for drugs that are positive reinforcers. Response rate maxima occurred at different unit doses in different animals (0.3-10 µg/kg/injection). Total intake of clonidine ranged to 3.4 mg/kg/session. The pattern of responding for intermediate doses of clonidine, though often evenly distributed over the session, was characterized by short bursts of responding followed by long pauses rather than the evenly spaced responding that was typical of cocaine self-administration. During periods of high clonidine intake, ptosis and sedation were observed in all animals.

TABLE 2

Intravenous Clonidine Self-Administration in Rhesus Monkeys Under Conditions of Unlimited Access in Different Phases of the Study

Monkey	Injections Per Session		Total Intake (µg/kg/day)	Incorrect Responses Per Session	
	Mean	Range	Mean	Mean	Range
Sessions 1-7 Saline 1.0 ml/inj					
3018	21	5-40	--	14	0-21
3147	125	89-182	--	18	4-22
Sessions 8-37 Clonidine 1.0 µg/kg/inj					
3018	23	5-73	23	18	3-87
3147	205	66-407	205	15	1-50
Sessions 38-76 Clonidine 5.0 µg/kg/inj					
3018	80	0-180	400	15	0-55
3147	180	42-411	900	3	0-19
Sessions 68-76* Saline 1.0 ml/inj					
3018	88(33)	8-527(98)	--	8	0-43
3147	53(45)	20-125(73)	--	1	0-5
Sessions 77-86 Clonidine 5.0 µg/kg/inj					
3018	181	84-324	905	7	2-16
3147	221	90-421	1105	4	0-21
Sessions 87-97* Saline 1.0 ml/inj					
3018	62(40)	19-289(68)	--	5	0-22
3147	101(83)	18-277(197)	--	1	0-5
Sessions 98-107 Clonidine 5.0 µg/kg/inj					
3018	248	166-302	1240	6	1-16
3147	447	204-763	2235	11	1-38
Session 108-117 Clonidine 1.0 µg/kg/inj					
3018	352	306-411	352	6	1-14
3147	388	157-550	388	2	0-6
Sessions 118-137 Clonidine 10 µg/kg/inj					
3018	223	157-339	2230	5	1-27
3147	358	14-877	3580	2	0-11
Sessions 138-147* Saline 1.0 ml/kg					
3018	73(55)	33-232(70)	--	2	0-13
3147	79 (48)	7-356(116)	--	1	0-5

*Data in parenthesis excludes extinction burst occurring on the first day of clonidine withdrawal.

Table 2 summarizes the results of unlimited access to clonidine for both subjects. The data are divided into periods of access to saline and 10-day segments of access to clonidine at various doses. During the first seven sessions of access to saline, the drug-experienced animal (#3147) took 125 injections/session while the drug-naive animal (#3018) averaged about 20 saline injections/session. During the initial 10 days of access to 1.0 µg/kg/injection clonidine, #3147 increased his rate of self-administration to 200 injections/session and maintained roughly this level of intake throughout this period. The second animal continued to take injections of this dose with the same frequency as he had saline. Total intake ranged between 30-240 µg/kg/session during this period. When the unit dose of clonidine was increased to 5 µg/kg/injection, both animals self-administered the drug at levels that were higher than saline. Monkey #3147 maintained his roughly 200 injection/session rate, thus increasing total intake five-fold to 800-1000 µg/kg/session. Monkey #3018 gradually increased clonidine intake over this period, often achieving daily intakes greater than 500 µg/kg. For both animals, as rates of responding for clonidine increased, the distribution of responding changed from responding primarily during the day to an even distribution throughout the session.

After a period (session 68-76) of access to saline during which responding declined to low levels, clonidine was again tested at several doses. Response rates were generally inversely related to unit dose. Animals usually averaged 350-400 injections/session at 1.0 µg/kg/injection. However, rates did not decrease in proportion to the increase in unit dose and overall intake increased dramatically at higher doses, often exceeding 2.0 mg/kg/day. After each period of access to saline, animals promptly resumed clonidine self-administration at or above previous levels within one session.

For both monkeys, initial high levels of clonidine intake produced ptosis and general slowing of reactions. Tolerance appeared to develop to this effect within 3-5 days. Food intake was unaffected by clonidine self-administration and the animals maintained good health.

When saline was substituted for clonidine (3 times during the experiment) a number of effects were apparent. During the first session of saline access, animals typically exhibited high rates of responding for saline (extinction burst). Saline access was continued for 9 additional days, and both animals responded at low levels during the last 8 sessions of each saline access period. Furthermore, several symptoms of withdrawal were clearly evident by four hours after drug termination and included restlessness, yawning, bruxism, facial flushing and wet dog shakes. Withdrawal symptoms that were prominent are summarized in table 3. Symptoms were most severe 8-12 hours after clonidine access was terminated and included marked facial flushing, excessive scratching, lying on side, refusal of preferred food,

vomiting and masturbation. Normal food intake was often reduced to less than 50% of control levels, particularly during the second and third withdrawal periods. Symptoms gradually became less severe with recovery to normal appearance by 72-96 hours.

TABLE 3

Incidence of Clonidine Withdrawal Symptoms

Symptom	Sessions 68-69		Sessions 87-88		Sessions 138-139	
Monkey	3147	3018	3147	3018	3147	3180
Facial Flushing	X	X	X	X	X	X
Scratching	X	X	X	X	X	X
Lying on Side	X	X	X	X	X	X
Masturbation	X	X	X	X	X	X
Piloerection	-	X	X	X	X	X
Extinction Burst	-	X	X	X	X	X
Salivation	-	X	X	X	X	X
Refused Preferred Food	X	-	X	X	X	X
Yawning	X	-	X	X	X	-
Wet Dog Shakes	X	X	-	X	-	X
Vomitus	X	X	-	-	-	X

During the second withdrawal period (session 87) clonidine (50 µg/kg) was administered intravenously and reversed the symptoms noted above. When naloxone (0.1 mg/kg, i.v.) was administered (session 86), no prominent symptoms were observed in #3147, though #3018 exhibited a severe reaction about 20 minutes after naloxone infusion characterized by symptoms observed at the height of the previous abrupt withdrawal. These symptoms were reversed by infusion of 50 µg/kg clonidine. However, these effects could not subsequently be replicated in either animal when saline, 0.1 and 0.3 mg/kg naloxone were administered on sessions 132, 133 and 134.

DISCUSSION

Based on the results from these two experiments, a few general statements can be made regarding intravenous clonidine self-administration in rhesus monkeys. Under conditions of limited or unlimited access clonidine was self-administered above saline levels and, at some unit dose, animals averaged 10-15 injections per hour. Generally, total intake was in the 0.1-1.0 mg/kg range though under unlimited access animals sometimes exceeded 5.0 mg/kg/day, In both situations, responding tended to occur in periodic bursts, followed by long pauses. Dose-reponses curves for clonidine were conspicuous in their "flatness." Under limited access, typical inverted "U" shaped functions were evident though response rates were not exceptionally high. At doses above those maintaining maximum rates, rates were generally inversely related to dose, although at higher unit doses

responding was not always suppressed. Similarly, with unlimited access there was generally an inverse relationship between dose and response rate, though there were clear exceptions to this rule. Self-administration was somewhat variable in both procedures, with wide ranges of intake and the effects of individual doses were not always replicable.

Generally, responding was more reliably above saline levels under conditions of unlimited access. A number of variables may contribute to this difference. Under conditions of unlimited access the development of tolerance and physical dependence may play a role in maintaining more reliable self-administration. Further, the relatively long duration of action of clonidine may contribute to the low rates under limited access. In addition, the low response cost under unlimited access (1 response/injection rather than 10 responses/injection) may be a contributing behavioral factor. Clonidine self-administration has been reported in rats as well (Shearman et al. 1977).

Under conditions of unlimited access physical dependence to clonidine was evidenced by characteristic symptoms of abstinence that were reversible by clonidine administration. These findings are consistent with those of Meyer et al. (1977) in rats with a daily clonidine dose of 250-350 µg/kg/day, though recovery in rats was somewhat more protracted than in the monkey. A number of the symptoms of clonidine withdrawal were similar to morphine withdrawal (diarrhea, lying on abdomen, ejaculation, bruxism). However, the dependence is evidently not of the morphine type since it could not be precipitated reliably by naloxone administration. This finding is in agreement with results of others that naloxone fails to reverse the acute effects of clonidine (Aghajanian, 1978; Fielding et al., 1978).

ACKNOWLEDGEMENTS

The research was supported by NIDA contract 271-77-3404. William L. Woolverton was a postdoctoral fellow supported by NIDA training grant DA-05164. William D. Wessinger was a predoctoral trainee supported by NIDA grant DA-01442. The authors wish to acknowledge the expert technical assistance of Earl E. Dowdy, Jr., and Kathleen T. Brady.

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Comparison of Discriminative and Reinforcing Effects of Ketamine and Related Compounds in the Rhesus Monkey

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One prominent behavioral characteristic of the dissociative anesthetics ketamine and phencyclidine is the ability to serve as discriminative stimuli. Phencyclidine shares discriminative properties with several of its structural analogues in rodents (Shannon, 1979) and with ketamine in pigeons (Herling et al., 1980). Moreover, a variety of narcotic mixed agonist-antagonists, such as cyclazocine and SKF 10,047, and dextrorphan, the dextroisomer of the narcotic levorphanol, share discriminative effects with phencyclidine and ketamine in these species (Herling et al., 1980; Holtzman, 1980). The phencyclidine discriminative stimulus is distinct from that of narcotic agonists, barbiturates, hallucinogens, and amphetamine in the rat (Shannon, 1979).

A second behavioral characteristic of ketamine and phencyclidine is the ability to function as a positive reinforcer (Balster et al., 1973; Pickens et al., 1973; McCarthy and Harrigan, 1976; Moreton et al., 1977). However, several drugs that share discriminative effects with phencyclidine in the rodent and pigeon, such as SKF 10,047, cyclazocine, and dextrorphan, do not serve as intravenous reinforcers for monkeys experienced with codeine (Hoffmeister, 1979; Woods, 1977; Woods et al., 1979). In order to characterize further the effects of ketamine and other compounds in the rhesus monkey, we directly compared the discriminative and reinforcing stimulus functions of ketamine with those of a variety of other drugs.

METHODS

Subjects. Rhesus monkeys in the self-injection study were given 75 gm of Purina Monkey chow 45 min prior to each experimental session; monkeys in the discrimination study were reduced to approximately 85 percent of their free-feeding weights and provided sufficient Purina Monkey Chow after each session to maintain their reduced weights. Fresh fruit was provided several times per week; isoniazid (40 mg/day) on sugar cubes was provided daily. Water was freely available in individual home cages.

Drug Discrimination Studies. Monkeys were trained to discriminate the subcutaneous injection of ketamine (1.0 - 1.8 mg/kg) under a procedure that has been described in detail elsewhere (Bertalmio et al., in press). Each monkey was trained to emit 100 consecutive lever press responses (fixed ratio 100; FR 100) on one of two levers in an experimental cubicle after an injection of ketamine and the same number of consecutive responses on the other lever after a sham injection. Completion of each FR 100 was followed by delivery of 3 gm of food. Daily sessions consisted of two to six discrete FR 100 trials, each separated by 10 min. The appropriate lever for a given trial was determined by the injection (ketamine or sham) that the animal received 10 min prior to the start of the trial. An injection of ketamine was given only once during each experimental session. During the two trials which followed the ketamine injection, responding on the ketamine-appropriate lever was reinforced. The two ketamine trials were preceded by from 0 to 4 sham injection trials.

After ketamine acquired discriminative control of responding, various drugs were tested for generalization to the ketamine stimulus. During generalization tests, monkeys received an increasing cumulative dose of the test drug 10 min prior to the start of each successive trial during the session. During each trial, 100 consecutive responses on either the ketamine-appropriate or the sham-appropriate lever resulted in food delivery. In general, testing continued until the monkey made 90 percent of its responses during a given trial on the ketamine-appropriate lever or until the rate of responding was markedly suppressed.

Intravenous Drug Self-injection Studies. Monkeys were conditioned to self-inject either codeine or ketamine, and the ability of test drugs to maintain self-injection behavior was evaluated under a substitution procedure (Woods, 1980). Monkeys were prepared with an indwelling siliconized rubber catheter implanted in a jugular, femoral, or brachial vein. To protect the catheter, each monkey wore a stainless steel harness (Deneau et al., 1969) connected to a jointed arm mounted to the back of the experimental cubicle. The catheter passed through the arm to an infusion pump. Monkeys lever pressed for intravenous drug injection during twice daily experimental sessions. During each session, lever pressing was maintained under a fixed-ratio 30 timeout 600 sec schedule of intravenous injection of either codeine (0.32 mg/kg /injection) or ketamine (1.0 mg/kg/injection). Each session terminated after 13 infusions or 130 min, whichever occurred first. During selected sessions, the maintenance dose of codeine or ketamine was replaced with saline or selected doses of test drugs. Two observations of each dose of each test drug were made in each of three monkeys.

Drugs. Codeine phosphate (S.B. Penick and Co., Lyndhurst, NJ), ketamine hydrochloride (Parke Davis and Co., Detroit, MI), phencyclidine hydrochloride (Dr. R. E. Willette, NIDA), dextrorphan tartrate and levorphanol tartrate (Hoffman-La Roche, Inc., Nutley, NJ), and SKF 10,047 hydrochloride (N-allyl-

normetazocine; Dr. A. Jacobson, NIH) were dissolved in 0.9% sterile saline. Dexoxadrol hydrochloride and levoxadrol hydrochloride (The Upjohn Company, Kalamazoo, MI) were dissolved in sterile water. Ethylketazocine methane sulfonate and cyclazocine base (Dr. W. Michne, Sterling-Winthrop Research Institute, Rensselaer, NY) were dissolved in sterile water to which a small amount of lactic acid was added. If needed, sodium hydroxide was used to adjust the pH of the solutions to between 3 and 4.

RESULTS

Drug Discrimination Studies. Ketamine acquired discriminative control over the monkeys' food-maintained lever pressing within 30 to 45 sessions. Ketamine doses of 0.56 to 3.2 mg/kg occasioned responding primarily on the ketamine-appropriate lever; lower doses occasioned responding on the sham-appropriate lever (Table 1). Phencyclidine, at doses of 0.1 to 0.32 mg/kg, also occasioned ketamine-appropriate responding; lower phencyclidine doses produced only sham-appropriate responding. Dextrorphan and dexoxadrol also produced dose-related responding on the ketamine-appropriate lever. Their levoisomers, levorphanol and levoxadrol, however, did not produce ketamine-appropriate responses at any dose tested, up to and including doses that decreased response rates. SKF 10,047 occasioned ketamine-appropriate responding at doses of 0.32 to 1.8 mg/kg. In contrast, cyclazocine, ethylketazocine, and codeine did not produce ketamine-appropriate responding at any dose tested, up to and including doses that severely suppressed response rates and precluded the delivery of food pellets.

Self-Self-injection Studies. Self-injection of the test compounds depended on the compound, its injection dose, and the baseline drug that maintained responding (Table 2). Codeine, 0.32 mg/kg/injection, and ketamine, 1.0 mg/kg/injection, maintained FR component response rates which ranged in individual monkeys from 0.9 to 2.7 and from 1.2 to 4.4 responses/sec, respectively. The monkeys usually received all 13 available infusions during maintenance drug sessions. Replacement of the maintenance drugs with saline for single sessions decreased response rates to 0.02 - 0.2 responses/sec and the number of injections to 3 - 8.

Ketamine and codeine maintained responding in all monkeys, independent of the maintenance drug (Table 2). The same doses of ketamine and codeine maintained maximal response rates for monkeys self-injecting either maintenance drug. On the other hand, phencyclidine, dextrorphan, and dexoxadrol maintained responses leading to their intravenous injection in monkeys experienced in self-injecting ketamine, but not in monkeys experienced in injecting codeine. When substituted for ketamine, injections of 0.03 mg/kg phencyclidine, 1.0 mg/kg dextrorphan, and 0.32 mg/kg dexoxadrol maintained responding leading to 12 or 13 injections per session, with response rates averaging 52, 50, and 58 percent of control rates, respectively. Higher and lower doses of each drug maintained response rates and infusion frequencies little

TABLE 1

Response generalization to test compounds by rhesus monkeys trained to discriminate ketamine from saline[a]

DRUG	DOSE RANGE	RESPONSES TO KETAMINE LEVER: LOWEST DOSE NECESSARY	MAXIMUM %
Ketamine	0.10-3.2	0.56	100
Phencyclidine	0.01-0.32	0.10	93 - 100
SKF 10,047	0.03-1.8	0.32	99 - 100
Dextrorphan	0.32-5.6	3.2	84 - 100
Levorphanol	0.01-0.32	---[b]	1
Dexoxadrol	0.10-3.2	1.0	98 - 100
Levoxadrol	0.32-17.8	---	1
Codeine	0.10-1.0	---	1
Ethyl-ketazocine	0.0003-0.018	---	2
Cyclazocine	0.003-0.1	---	3

[a]Data represent values for one test in each of two monkeys.
[b]Compounds did not occasion ketamine-appropriate responses at any dose.

higher than those maintained by saline. The highest phencyclidine and dextrorphan doses produced ataxia and salivation in all subjects. When phencyclidine, dextrorphan, or dexoxadrol were substituted for codeine, however, no injection dose maintained response rates or injection frequencies higher than those maintained by saline.

SKF 10,047 did not maintain responding by either ketamine- or codeine-experienced monkeys. Cyclazocine did not maintain responding by codeine-experienced monkeys. In ketamine-experienced monkeys, 0.001 mg/kg cyclazocine injections maintained rates averaging 10% of those maintained by ketamine. Lower and higher cyclazocine doses maintained rates no higher than those maintained by saline. At the highest SKP 10,047 and cyclazocine injection doses (0.32 and 0.032 mg/kg, respectively) both ketamine- and codeine-experienced monkeys took only one to three injections and did not approach the lever during the remainder of the 130 min experimental session.

DISCUSSION

The dissociative anesthetic ketamine shared interoceptive effects with an interesting variety of compounds, including phencyclidine,

TABLE 2

Maximum response rates and injections, expressed as a percent of control, maintained by test drugs in individual monkeys experienced in self-injecting codeine or ketamine[a]

TEST DRUG (range of injection doses, mg/kg)	INJECTION DOSE (mg/kg)	MAINTENANCE DRUG: CODEINE Response rate	CODEINE Injections	KETAMINE Response rate	KETAMINE Injections
Codeine (0.032-1.0)	0.32			22[b]	96[b]
				52	100
				87	100
Ketamine (0.01-3.2)	1.00	46	92		
		114	100		
		117	100		
Phencyclidine (0.01-0.10)	0.03	1	27	23	96
		5	50	77	100
		12	65	79	100
Dextrorphan (0.01-3.2)	1.00	2	15	35	100
		2	46	41	96
		20	88	42	96
Dexoxadrol (0.032-1.0)	0.32	2	54	42	100
		3	42	52	100
		8	77	73	100
Cyclazocine (0.0001-0.032)	0.001	1	19	2	58
		1	38	13	88
		2	35	13	92
SKF 10,047 (0.01-0.32)	---[c]	1	35	1	27
		2	31	1	38
		3	54	3	35
Saline[d]		5 (2.2-9.6)	50 (37-62)	3 (2.1-6.3)	57 (43-67)

[a]Control rates and injections maintained by maintenance drugs are given in text.
[b]Entries are data for individual monkeys.
[c]No injection dose of SKF 10,047 maintained rates or injection frequencies higher than those maintained by saline. Data are for 0.1 mg/kg/injection.
[d]Mean and range of average data for all monkeys studied are shown.

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dextrorphan, dexoxadrol, and SKF 10,047. In turn, phencyclidine,. dextrorphan and dexoxadrol were self-administered by monkeys with recent experience self-administering ketamine. SKF 10,047, however, was not self-administered by ketamine-experienced monkeys.

The similarity of the discriminative effects of ketamine with those of phencyclidine, dextrorphan, and SKF 10,047 in the monkey agrees with results reported for pigeons and rodents (Herling et al., 1980; Holtzman, 1980). The results with cyclazocine in the monkey, however, differ from those reported for other species: Cyclazocine did not produce ketamine-appropriate responding in the monkey, but produces phencyclidine- or ketamine-appropriate responding in rats and pigeons (Holtzman, 1980; Herling et al., 1980). The lack of ketamine-appropriate responding produced by codeine, levorphanol, levoxadrol, and ethylketazocine agrees with data in the pigeon (Herling et al., 1980, unpublished observations).

Ketamine and codeine served as intravenous reinforcers in all monkeys, and cyclazocine and SKF 10,047 in none. Phencyclidine, dextrorphan, and dexoxadrol, however, served as reinforcers in monkeys experienced with ketamine, but not in monkeys experienced with codeine. The similarity of the interoceptive effects of ketamine to those of phencyclidine, dextrorphan, and dexoxadrol in the monkey may be responsible for the latter three compounds' capacity to serve as reinforcers in ketamine-experienced monkeys. It remains to be determined whether recent exposure to ketamine or longer exposure to phencyclidine, dextrorphan, or dexoxadrol will increase the reinforcing efficacy of these compounds in codeine-experienced monkeys. The failure of SKF 10,047 to serve as a reinforcer in monkeys experienced in self-injecting ketamine, with which it also shares discriminative effects, emphasizes, however, that the classification of compounds with respect to their discriminative similarity to ketamine may not unequivocally predict their ability to exert other actions characteristic of ketamine, i.e., to serve as intravenous reinforcers.

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ACKNOWLEDGMENTS

Reseach supported by National Institute on Drug Abuse Grants DA 00254, DA 00154, and DA 02230.
We thank Dr. Kenneth R. Stephens, Gail A. Renard, Thomas R. Ward, and Kathi L. Watson for excellent technical assistance.

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A Pharmacologic Comparison Between Phencyclidine, Its Precursor, Metabolites, and a Quaternary Derivative in the Dog

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INTRODUCTION

Studies in the chronic spinal dog have demonstrated that the effects of single doses of phercyclidine are remarkably similar to those reported in man, indicating that the dog offers promise as a valid model to study phencyclioine-type compounds (Jasinski et al., 1979; Jasinski et al., in press). Further, by compiling both the physiologic and behavioral effects of drugs to form pharmacologic profiles in the dog, phencyclidine was clearly distinguishable from other types of hallucinogens (i.e., LSD, Δ^9-tetrahydrocannabinol ard d-amphetamine) except for the hallucinogenic opioid N-allylnormetazocine (SKF 10,047). The present investigations evaluated the basic pharmacologic actions of four compounds structurally related to phercyclidine: 1) 1-(1-phenylcyclohexyl)piperidine methiodide (PCPMeI), 2) 1-(1-phenylcyclohexyl)-4-hyoroxypiperidins (PCHP), 3) 4-phenyl-4-piperidinocyclohexanol (PPC), and 4) 1-piperidinocyclohexanecarbonitrile (PCC).

The quaternary analogue of phencyclidine, PCPMeI, was used as a pharmacologic tool to separate the peripheral and central actions of phercyclidine, based on a theoretical difficult entry for PCPMeI into the CNS. Previous metabolic studies in the dog have demonstrated that phercyclidine is hydroxylated in one of two positions resulting in the production of PCHP and PPC with the latter predominating (Core et al., 1980). Aside from the convulsant properties of the metabolites (Domino, 1978); their pharmacology has not been studied systematically. Consequently, the actions of the metabolites were compared to those of phencyclidine and potency estimates were made when possible. PCC is the synthetic precursor of phencyclidine, and two reports (Jasinski et al., 1979) of its effects were presented to the CPDD last year. In brief, rotarod studies using ataxia in the mouse were unable to differentiate phencyclidine and PCC, except on the basis of potency, whereas they were readily differentiated using the rat discriminative stimulus paradigm. As a result we sought to characterize the pharmacological actions of PCC in the dog in an attempt to differentiate it from phercyclidine and thereby further validate the dog as an animal model for the study of phercyclidine.

METHODS

Previous publications (Martin et al., 1978; Vaupel et al., 1977) have described the methods in detail using the chronic spinal dog. In the present studies five female chronic spiral dogs were used in a crossover experiment. Drug and vehicle treatments were incompletely randomized. The hindlimb flexor reflex was elicited by a pneumatic toe pincher which randomly administered either a low (4.5 psi), medium (9 psi) or high (18 psi) pressure stimulus. Other parameters treasured included respiration, heart rate (measured from an EKG), pupil size, nictitating membrane width, the skin twitch reflex, temperature, and general behavioral activity. Nonparametric measures included vocalizations, stereotypic head and eye movements, attentiveness to external stimuli, and the presence of both the medial and lateral canthus reflexes.

Each 100-min experiment was divided into a 30-min control period, a 40-min i.v. infusion (of drug or vehicle control) into the cephalic vein, and a 30-min postinfusion period. With the exception of the flexor reflex, which was evoked at 1 min intervals, and temperature, which was taken rectally at the beginning and end of each experiment, measurements were made at 10-min intervals throughout the experiment. Time-action curves were plotted for each parameter and areas (30-100 min) under the curves were calculated for statistical comparison using paired t-tests. A chi square analysis was used to test nonparametric measures. Results were considered to be significant at the $p < .05$ level or higher. Cumulative dose-response curves were produced by taking that portion of a time-action curve generated during the infusion and using the four cumulative doses coinciding with the 10, 20, 30, and 40 min times of the infusion with the corresponding response.

Selection of the 0.5 mg/kg test dose of phercyclidine was based upon a previous study. The limited quantity of PCPMeI necessitated the use of only a 0.69 mg/kg dose which was equimolar to phencyclidine. Numerous preliminary experiments were used to select nonconvulsant doses of PCHP (4 mg/kg), PPC (10 mg/kg), and PCC (6 mg/kg). The following vehicles were used: 1) saline for phenyclidine HCl and PCPMeI, 2) double distilled water adjusted to pH 4 for the free base form of PCC, and 3) a 3:2 ratio of 8.5% lactic acid in in NaOH for the free base forms of PCHP and PPC. Vehicle control experiments were run for saline and the lactic acid-NaOH solution.

RESULTS

Phencyclidine and Phencyclidine Methiodide (PCPMeI)

Phencyclidine (0.5 mg/kg) produced its expected characteristic pharmacologic profile of activity without any convulsant activity. Compared to saline, phencyclidine (Fig. 1) depressed the flexor reflex, produced marked increases in heart rate, pupil

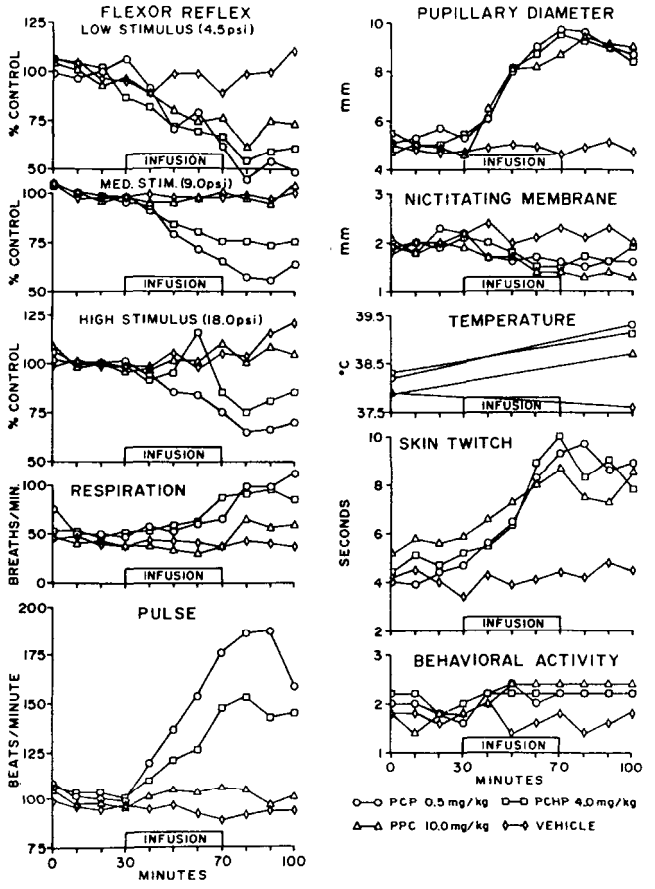
size, the latency of the skin twitch reflex, lacrimation, rhinorrhea, and salivation plus a moderate hyperthermia. Under the influence of phencyclidine the dogs became slightly, but significantly more restless, which differed from their quiet behavior observed in the control period. Other behavioral signs comprising the phencyclidine profile were nystagmus, tracking and staring (with staring being predominant), stereotyped head rocking movements, failure to attend to external stimuli in the laboratory and loss of the lateral canthus reflex to gentle touching. Opisthotonic posturing was not a significant finding in these experiments. This is in contrast to its development in a previous study using the same dose. Saline was without effect.

When administered in a dose equimolar to phencyclidine, PCPMeI was almost inactive. Among the physiologic measures, the only significant effects of this quaternary amine with respect to saline were small increases in the latency of the skin twitch reflex and in the size of the nictitating membrane indicating it was more relaxed. The analgesic effect of the methiodide compound as assessed by the delay in the onset of the skin twitch reflex (1.7 sec) was much smaller ($p < .05$) than the corresponding effect of phencyclidine (5.0 sec) at the 70-min mark of the experiment. The effects of these two drugs on the nictitating membrane did not differ from each other. Supplementing the relatively minimal physiologic responses was a complete absence of behavioral responsiveness to PCPMeI.

The Hydroxylated Metabolites: 1-(1-Phenylcyclohexyl)-4-hydroxypiperidine (PCHP) and 4-Phenyl-4-piperidinocyclohexanol (PPC).

The choice of a 4 mg/kg aose of PCHP and a 10 mg/kg dose of PPC was based on their ability to produce the same degree of mydriasis as 0.5 mg/kg of phencyclidine. As illustrated in figure 1, both metabolites and phencyclidine shared the ability to dilate pupils, increase body temperature, prolong the latency of the skin twitch reflex as well as increasing lacrimation, rhinorrhea and salivation. PCHP, PPC and phercyclidine all retracted the nictitating membrane slightly, but the effect of phencyclidine did not attain significance. There were no charges in respiration. Among the other physiologic measures, heart rate showed the most divergent effects (Fig. 1). Most apparent was the lack of effect of PPC on heart rate, which contrasted sharply with the phencyclidine-induced tachycardia. The degree of tachycardia produced by PCHP occupied an intermediate position with respect to PPC and phemyclidine. Regression analysis demonstrated that the flexor reflex elicited by the low pressure stimulus decreased linearly throughout the infusion and postinfusion periods with phemyclidine and both metabolites but not with the saline or lactic acid vehicles (Fig. 1). However, area comparisons for these same curves indicated that only the reflex depression produced by PPC differed from control values. when the flexor reflex was elicited by the medium and high pressure stimuli, phemyclidine but neither PCHP nor PPC was statistically effective in producing reflex depression (Fig. 1).

FIGURE 1



Pharmacologic effects of 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (PCHP), 4-phenyl-4-piperidinocyclohexanol (PPC), and phencyclidine (PCP) in the chronic spiral dog. The effects of the lactic acid-NaOH vehicle for PCHP and PPC did not differ from those of saline (PCP vehicle) which are not graphed. Each time-action curve represents the mean responses of 5 dogs.

With respect to behavior all three drugs made the dogs more restless. Additional features produced by phencyclidine and PCHP included nystagmus, staring, stereotypic head movements and loss of attentiveness. Of these four signs, PPC elicited only the stereotyped head movements. However, instead of nystagnus, PPC produced rapid eye movements, a characteristic associated with amphetamine-like compounds.

fly selecting corresponding sections of the cumulative dose-response curves, valid potency estimates (Table 1) were obtained from parallel-line bioassays for the flexor reflex (low stimulus), pupillary diameter, pulse rate and latency of the skin twitch reflex. Generally, PCHP was about 1/8 as potent and PPC approximately 1/20 as potent as phencyclidine.

TABLE 1

Measure: Effect:	Flexor Low Stim Reflex Depression	Pupils Mydriasis	Pulse Tachycardia	Skin Twitch Increased Latency
PCHP	.15(0-.46)	.12(.05-.20)	.07(.004-.18)	.14(.05-.23)
PPC	.04(0-.16)	.05(.01-.10)	No Effect	.06(0-.20)

Relative potencies with their 95% confidence limits in parentheses were obtained from valid bioassays. Relative potency is defined as the mg of phencylidine HCl equivalent to 1 mg of the test compound. Depression of the flexor reflex and increased latency of the skin twitch are used as measures of analgesia.

The Precursor: 1-Piperidinocyclohexanecarbonitrile (PCC)

At the end of the PCC infusion significant effects included tachycardia (163 beats/min), small increases of 35 breaths/min in respiratory rate and 0.9 mm in pupillary diameter, staring and head raising. These changes were short-lived as they were no longer significant at the end of the experiment. Additionally, there were slight, though nonsignificant, increases in lacrimation, rhinorrhea, salivation and restlessness. Those actions which were both qualitatively and quantitatively similar to PCP were the tachycardia and staring, whereas qualitative similarities were present as the slight mydriasis and the increase in secretory activity of the eyes, nose and mouth. Phencyclidine-like actions which were obvious by their absence from the PCC data included depression of the flexor reflex, a prolonged latency of the skin twitch reflex, hyperthermia, nystagmus, stereotype, loss of attentiveness to external stimuli and the disappearanace of the lateral canthal reflex.

While lacking statistical significance, a number of other effects produced by PCC were noteworthy insofar as they were not observed at all with phenyclidine or its metabolites. First, three dogs developed the stepping reflex or fragmentary stepping for small periods of time. Second, two animals vomited during the infusion and another retched. Third, the white portions of the skin found on the abdomen and on the shaved areas surrounding the EKG leads became conspicuously pink during the infusion of PCC. Upon terminating the infusion the pinkness disappeared.

DISCUSSION

Con-pared to phercyclidine, intravenously administered PCPMeI was almost devoid of pharmaccologic activity in the chronic spinal dog. Similar findings have been reported by Kalir et al. (1978). Our data suggest that most of the effects of phencyclidine orginate at central sites of action. This finding is limited to the extent that we have not tested higher doses of PCPMeI to ascertain the relative effectiveness of the blood brain barrier, nor has the direct central administration of PCPMeI into the ventricles been attempted in order to reproduce phencyclidine-like activity.

The hydroxylation of phencyclidine to form less potent metabolites is consistent with established pharmacologic principles. PPC was less active, being approximately 2 1/2 times less potent than PCHP. In view of this potency difference it is apparent that it is more advantageous to detoxification that the dog produce greater quantities of PPC than PCHP, as shown by Cone et al. (1980).

Composite pharmacologic profiles were developed for the two monohydroxylated metabolites of phencyclidine. On the whole, the profile for PCHP was similar to that of its parent compound and thus was classified as a phencyclidine-like drug. However, the qualitative differences between the profiles of phencyclidine and PPC were numerous enough to conclude that PPC is not primerily a phencyclidine-type compound. Our conclusion that PPC is pharmacologically different from phencyclidine is in agreement with the discriminative stimulus studies of Shannon in which rats trained on phencyclidine did not show stimulus generalization to PPC (Jasinski et al., in press).

The precursor of phencyclidine, PCC, failed to reproduce most of the effects characteristic of phercyclidine, thereby clearly differentiating it from phencyclidine on the basis of its profile of action. Bailey et al. (1976) have hypothesized that the toxic properties of PCC, sometimes found as a contaminant in street phencyclidine, could be attributed to the in vivo generation of hydrogen cyanide. Several effects observed in this study lend support to this hypothesis and were consistent with a low level of cyanide toxicity. These signs, while not pathognomonic, included emesis, rapid heart rate and a flushing of the skin which we postulated to be due to the hyperoxygenation of the blood (Chen and Rose, 1952; Hatch, 1977).

In summary, the lack of activity of PCPMeI is suggestive that phencyclidine acts primarily centrally. PCHP and PPC, the primary metabolites of phercyclidine, were less potent than phencyclidine. The pharmacologic profile of PCHP was identical to that of phencyclidine whereas that of PPC was not. To our knowledge only a single report of a pure sample of the phencyclidine precursor PCC has appeared oh the street suggesting that it has a low level of acceptance as a drug of abuse in man.

Together the information obtained from the dog, rat and man argue that the pharmacology of PCC is not rat like that of phencyclidine and further validates the dog as an effective animal model to identify phencyclidine-type compounds.

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Phencyclidine Inhibition of Cerebellar Purkinje Neurons

J. Marwaha, M. Palmer, B. Hoffer, and R Freedman

Recent Drug Abuse Warning Network statistics indicate that phencyclidine (PCP) is incriminated in 25 percent of all cases of psychedelic drug abuse. Among its psychotomimetic effects, PCP profoundly alters normal sensory perception, and the resulting psychosis closely resembles naturally occurring schizophrenia (Balster and Pross, 1978). It is postulated that PCP may elicit these behavioral changes via an interaction with bicgenic amine transmitters in the brain. There exist few reports of electrophysiological actions of PCP on identified neurons to test this hypothesis. Since the rat cerebellum is a brain region where cell types and pathways can be identified during recording, and the identity of putative transmitters to various neurons in the region is well established (Freedman, 1977), we undertook the study of PCP in this region.

METHODS

Male Sprague-Dawley rats were anesthetized, intubated and placed in a stereotaxic frame. After appropriate surgery, the brain surface was covered with agar. Body temperature was maintained at 37° C. Five-barreled micropipettes were used to record extracellular action potentials of spontaneously active single Purkinje neurons and to apply substances at the site of recording. Some drugs (e.g., GABA and NE) were applied by conventional iontophoresis whilst other drugs (e.g., PCP, ketamine and haloperidol), not sufficiently polar or soluble for microiontophoresis, were applied by pressure ejection. Both iontophoresis and pressure ejection, used in our laboratory, yield reproducible dose response relationships.

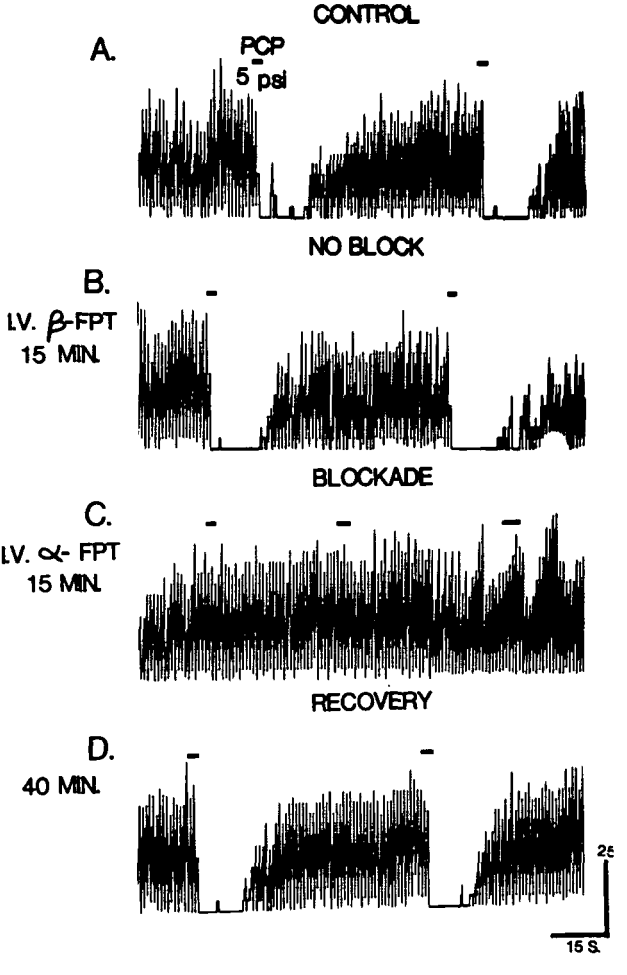
Extracellular action potentials were amplified, monitored on an oscilloscope, and converted to constant voltage pulses by a window discriminator. The pulses were fed to a ratemeter which integrated them over one-second intervals for display on a strip chart recorder. Further details of the procedures employed may be obtained from our previous papers (Marwaha et al. 1980, a,b; Freedman and Marwaha, 1980).

RESULTS

PCP and its less potent analog, ketamine reversibly depressed the firing of Purkinje cells. The EC_{50}'s for the 2 compounds were 3.5 and 18 PSI-sec, respectively. Haloperidol (a butyrophenone antipsychotic drug), administered intraperitoneally, antagonized the depressant effects of PCP and ketamine. Since parenteral administration of haloperidol could have remote or indirect effects, the antipsychotic was locally applied. When haloperidol was locally applied, it also consistently blocked the effects of PCP.

To determine the specificity of the antagonism, inhibitory effects of PCP were studied before and after administration of alpha-flupenthixol (a potent neuroleptic), and beta-flupenthixol (an inactive isomer). Beta-flupenthixol given systemically did not block PCP-induced inhibitions, whereas alpha-flupenthixol did (Figure 1).

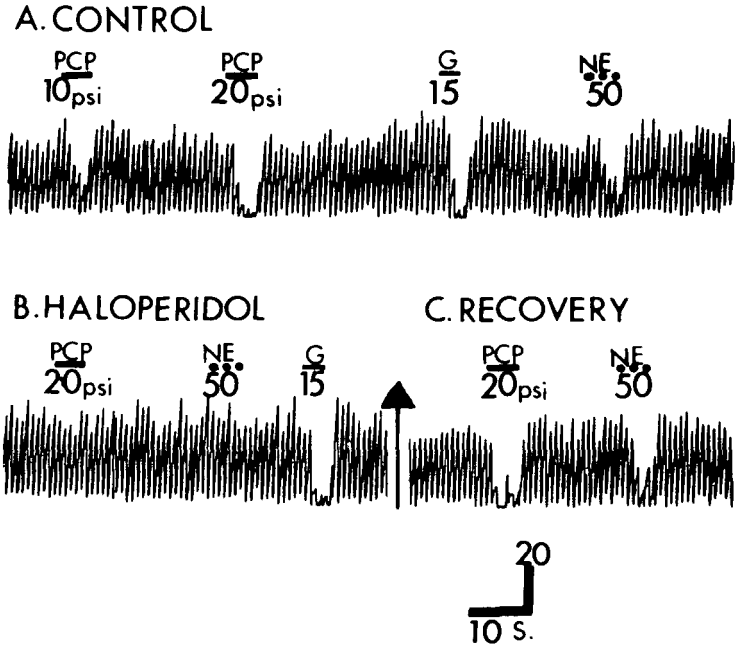
FIGURE 1



Ratemeter record of PCP actions on a single Purkinje cell. PCP causes profound inhibition (A), and this inhibition is still present when β-flupenthixol (β-FPT) is administered intravenously (B). Inhibitory actions of PCP are blocked 15 min. after administration of α-flupenthixol (α-FPT) intravenously (C). 40 min. after administration of α-FPT, there is complete recovery to the inhibitory effects of PCP.

We have previously shown that norepinephrine (NE) and GABA also depress Purkinje neuron discharge. NE responses but not GABA effects are blocked by antipsychotics (Freedman, 1977). In the current study, parenterally administered haloperidol blocked the inhibitory effects of norepinephrine and PCP, but not those of GABA (Figure 2).

FIGURE 2

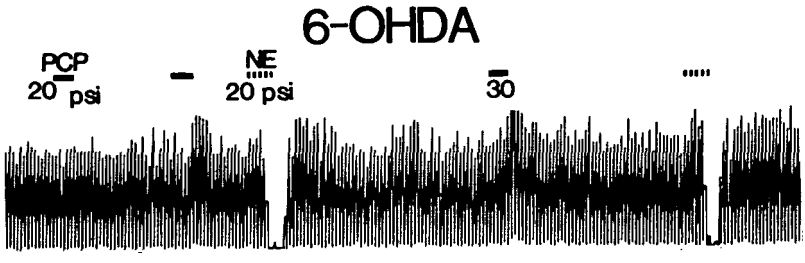


Ratemeter record of inhibitory actions of PCP, GABA (G) and norepinephrine (NE) on a single Purkinje cell (A). The inhibitory actions of PCP and NE, but not those of G are antagonized 45 min. after administration of haloperidol (B). 90 min. after administration of haloperidol, there is complete recovery to the inhibitory actions of PCP and NE (C).

Histofluorescent, ultrastructural and biochemical studies have shown that intracistemal 6-hydroxydopamine (6-OHDA) treatment produces a nearly totalandirreversible destructionof cere-

bellar noradrenergic afferents (Bloom et al. 1969). Interneuronal excitatory (granule cell-parallel fiber) and inhibitory (basket-stellate cell) pathways to the Purkinje cell in the cerebellar cortex can be destroyed by neonatal degranulation with X-irradiation (Woodward et al. 1974). After treatment with 6-OHDA, Purkinje cells are no longer depressed by local ejection of PCP (Figure 3).

FIGURE 3



Effects of PCP (solid line) and NE (dotted line) on P cell discharge after pretreatment with 6-OHDA. Note that there is no effect of PCP at a dose much higher than that required in normal rats, whereas a similar ejection of NE induces a maximal depression. The vertical and horizontal calibrations for this figure are the same as for Figure 1.

In contrast, Purkinje neurons from neonatally X-irradiated animals manifest normal responsivity to this substance. The effects of PCP on spontaneous firing of Purkinje neurons from variously treated rats are described in Table 1.

TABLE 1

	Excite	Depress	No Effect
Control Bats	2	46	3
6-OHDA Rats	2	2	17
X-Irradiated Rats	1	9	1
X-Irradiated + 6-OHDA Rats	1	0	8

DISCUSSION

This investigationhas shown that PCP inhibits the spontaneous discharge of Purkinje cells, and its inhibitory effects are blocked in a rapid, reversible and specific fashion by antipsychotic drugs. Previously, our laboratory (Freedman, 1977) has shown that neuroleptics specifically block norepinephrine-induced inhibitions in the cerebellum. Since the effects of PCP and NE, but not those of GABA were antagonized by antipsychotic drugs, it may be hypothesized that norepinephrine is involved in the actions of PCP. Supporting this conjecture, several investigators

have shown sympathomimetic properties for PCP (Chen et al. 1965; Smith et al. 1977; Fessler et al. 1979). After neonatal X-irradiation which destroys cerebellar interneurons and consequently parallel fiber excitatory and basket-stellate GABAergic inhibitory pathways, little change is seen in PCP effects. In contrast, selective destruction of cerebellar NE-containing afferentswith 6-OHDA completely eliminates responses to PCP. Such findings strongly support the hypothesis that PCP-induced depressions of cerebellar Purkinje neurons are mediated by presynaptic NE release fran noradrenergic fibers synapsing onto Purkinje neurons.

The finding of a central sympathomimetic effect for a psychotomimetic drug provides further evidence for the participation of noradrenergic mechanism in the sensory disturbances which accompany psychosis. We have previously shown that NE increases the sensitivity of Purkinje neurons to afferent climbing and mossy fiber synaptic input (Freedman, 1977). Neuroleptics, by blocking the effects of NE, would cause neurons tobeless affected by their afferent inputs. Our studies do not preclude the interactions of PCP with other transmitter system. These reservations notwithstanding, however, the fact that the efficacy of PCP and ketamine in slowing Purkinje discharge parallels their psychotomimetic potency, and that both behavioral and electrophysiological actions are antagonized by antipsychotics, suggest that the neuronal responses reported here may relate to the sensory and psychotic disturbances produced by these psychotometic drugs.

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The California Registration System for Habitues to Schedule II Drugs

F. S. Tennant, Jr.

SUMMARY ABSTRACT

In order to help control abuse and prevent over-prescribing, California has developed triplicate prescriptions for Schedule II narcotics as well as a system for physicians to publicly register patients who are habitues to Schedule II Controlled Substances. A preliminary evaluation indicates that there is under-reporting and confusion among physicians about the system, but it has probably helped control Schedule II narcotic abuse in California while not depriving patients of needed treatment. Physicians appear to prescribe Schedule II narcotics for serious medical conditions but may underprescribe narcotics for some chronic pain patients and subject others to potential complications of high, chronic doses of oral narcotics which are combined with salicylate, acetaminophen, or phenacetin. Despite some defects, California's system of triplicate prescriptions and public registration of habitues appears a viable alternative to the removal of abusable, Schedule II drugs from the commercial market.

INTRODUCTION

Abuse of prescription drugs is a matter of great concern.[1-4] A major regulatory effort to control abuse of prescription drugs has been the Comprehensive Drug Abuse Prevention and Control Act of 1970 which classifies abusable prescription drugs into five schedules. Drugs in the lower (III, IV, and V) schedules have fewer prescribing restrictions than those in the upper (I and II) schedules. Five states, including California, have adopted a triplicate prescription system for Schedule II narcotics. With this system the physician and pharmacist each retain a copy of the prescription and one copy is forwarded to State authorities to allow monitoring of over-prescribing and identification of prescription "shopping" by patients.

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California has developed an additional mechanism to reduce abuse of Schedule II drugs. Any physician prescribing or furnishing a controlled substance classified in Schedule II to an habitual user is to report the patient in writing to the Office of the California Attorney General. Described here is the first study of this system to determine if physicians use the system properly and to help assess its effectiveness in controlling abuse of Schedule II drugs.

DESCRIPTION OF THE REPORT SYSTEM

The report, which the physician files with the State, must contain the following:

- Name of the patient
- Address of the patient
- Character of the injury or ailment
- Quantity and kind of controlled substance used
- A statement as to whether or not the patient is an addict

For ease in reporting the above information, the California Department of Justice has developed a 3" by 5" preprinted, "patient report card". (Figure 1) This information is then used to identify patients who go from physician to physician to obtain Schedule II drugs for non-medical use and to protect the physician and patient who appropriately use Schedule II drugs.

METHODS

In 1979 the Bureau of Narcotic Enforcement of the California Department of Justice granted the author access to data from the patient report cards submitted by all California physicians beginning November 1, 1979. All required reporting information was available except the names of the patients and physicians. This review covers the 7-month period from November 1, 1979 through June 1980.

RESULTS

A total of 224 patients were registered in this period. Schedule II narcotics accounted for 167 (74.6 percent) of the cases, and they were prescribed for medical conditions which are well-recognized to be associated with severe, chronic pain. (Tables One and Two) The most common reasons to prescribe narcotics were carcinoma, arthritis, headaches, lumbo-sacral disease, and post-traumatic pain. Maximum daily dosages of narcotics generally appeared to be compatible with mild forms of addiction.[5] Only 19 (8.4 percent) of the cases were for habitues to non-narcotic Schedule II drugs. The most common drugs prescribed were barbiturates and methylphenidate. Barbiturates were usually prescribed for insomnia and methylphenidate for hyperactivity or learning disorder.

Thirty-eight (17.0 percent) cases did not need to be registered because they were prescribed codeine compounds, propoxyphene, diasepam, pentazocine, or another drug which is not in Schedule II.

DISCUSSION

Findings in this review of limited data indicate under-reporting and confusion about reporting requirements. Although approximately 350,000 triplicate prescriptions for Schedule II narcotics were written in California in this 7-month period, only 167 patients were classified as habitues to Schedule II narcotics by physicians and registered with the State. An additional 57 patients who were prescribed drugs other than Schedule II narcotics were classified as habitues and registered. Although the number of habitues to Schedule II drugs in California is unknown, the number must surely be greater than the number registered considering that epidemiologic surveys indicate that 5 to 10 percent of general medical patients regularly use one or more psychoactive prescriptions drugs.[2,6]

Many physicians are obviously confused about the California reporting system. Thirty-eight (38) of the 224 (17.0 percent) registered persons didn't need to be registered since a Schedule II controlled substance wasn't prescribed. Very few (19; 8.4 percent) non-narcotic Schedule II habitues were registered. In California, Schedule 11 non-narcotic drugs do not require a triplicate prescription in contrast to Schedule II narcotic drugs. Apparently the fact that Schedule II non-narcotic drugs don't require a triplicate prescription indicates to the majority of physicians that registration is not necessary for habitual users. Some under-reporting may occur because the definition of "habitue" is not precisely defined in the Uniform Controlled Substances Act of California; therefore, the physician must determine this.[7]

Most of the narcotics prescribed to habitues were oxycodone or codeine compounds which contain the potentially toxic substances acetaminophen, salicylate, or phenacetin. High doses of these compounds are of concern due to the potential liver toxicity of acetaminophen, renal toxicity of phenacetin, and gastrointestinal bleeding from salicylates.[8-11] Plain codeine or another narcotic in a habitual, high-dose user avoids these potential complications. The dosage of narcotics did not appear particularly high in some cases, and the question of adequate pain relief is suggested since this is a common clinical occurrence.[10,12]

Despite the problems noted above, it appears that this system has probably helped control abuse and indiscriminate prescribing of Schedule II narcotics in California while allowing habitual use and humanitarian pain relief. Less than 5 percent of physician arrests for prescribing violations in California have been for narcotics, while approximately 20 percent have been for narcotics in the rest of the United States.[13] A campaign to educate physicians about the system could make it much more

effective and still not deprive of treatment patients who may benefit from potentially abusable Schedule II drugs. The California system of triplicate prescriptions plus public registration of habitues appears, therefore, to be a viable alternative to the removal of any Schedule II drugs from the commercial market.

TABLE ONE
CASES OF SCHEDULE II NARCOTICS
REGUIRING REGISTRATION
N = 167

Drug	Number	Age Range (Yrs.)	Mean Age (Yr.)	Maximum Daily (Mgs) Dosage Range	Mean Daily Maximum Dosage (Mgs)
Oxycodone	77	26-92	58.0	10-105	32.2
Hydromorphone	33	22-86	50.9	4-40	16.3
Meperidine	18	34-95	59.9	50-800	343.2
Methadone	17	18-89	48.7	20-120	45.9
Codeine	11	19-68	34.2	60-900	470.0
Morphine	9	34-75	51.3	15-720	265.0
Levorphanol	1	26	26	2	20.0
Anileridine	1	63	63	50	50.0

TABLE TWO
MEDICAL CONDITIONS REQUIRING REGISTRATION
FOR HABITUATION TO SCHEDULE II NARCOTICS
N = 167

Condition	No.
Osteomyelitis	3
Seizure Disorder	2
Biliary Atresia	1
Abdominal Pain	1
Psychologic/Unknown	10
Detoxification	4
Chronic Cystitis	1
Gaucher's Disease	1
Multiple Sclerosis	1
Buerger's Disease	1
Chronic Obstructive Pulmonary Disease	1
Tooth Abscess	1
Carcinoma	49
Lumbo-Sacral Disease	13
Post-Traumatic Pain	16
Headaches	15
Arthritis/Bursitis	19
Post-Surgical Pain	13
Neuropathy/Neuralgia	3
Angina Pectoris	4
Regional Enteritis	2
Chronic Pancreatitis	3
Ulcerative Colitis	1
Inoperable Renal Calculi	1
Total	167

FIGURE ONE
THE CALIFORNIA "PATIENT REPORT CARD"
FOR HABITUES TO SCHEDULE II DRUGS

BUREAU OF INVESTIGATION & NARCOTIC ENFORCEMENT
State of California
Mail to: 874 Town & Country Rd., Ste. 110,
Orange, California 92668

Name of Patient _____ Age _____

Address _____
Street City

Quantity and Kind of Narcotic _____

Daily Dosage _____

Diagnosis of Injury or Ailment _____

Has Patient Previously Used Narcotics? _____ Addicted? _____
Yes or No Yes or No

Physician's Signature _____

Address _____
Street City

Date of Report _____ Fed. Reg. No. _____

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ACKNOWLEDGEMENTS

The Bureau of Narcotic Enforcement, California Department of Justice, Chief S. C. Helsley granted approval for this study. W. G. Walker is special assistant to the project.

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The Effects of Law Enforcement Activity on a Population of Opiate Abusers

C. A. Atkinson

This study examined the effect of police action against heroin pushers on clients of methadone programs in metropolitan Denver. On November 10, 1979, twenty suspected drug dealers and buyers were arrested and another twenty were under investigation in a vice squad operation in metropolitan Denver. The operation involved an undercover agent who mingled with addicts and bought opiates over an extended period from dealers, who were later arrested within a 48-hour period. Newspaper reports indicated that most of those arrested had been selling heroin in the vicinity of the outpatient clinic operated by Addiction Research and Treatment Services (ARTS) of the University of Colorado School of Medicine. Although linked to the clinic by the press, only two of those arrested were known to clinic personnel. In this study we examined the patterns of opiate use of the clients enrolled in that clinic as reflected by the presence of opiate metabolites in their urine samples collected before and after the drug bust. The clinical course of a sample of clients who abused opiates before, but not after the bust was examined. In addition, urine data from the other two methadone programs in the city were examined.

Metropolitan Denver has a population of 1.5 million and is approximately 500 miles from any population center of similar size. Drugs confiscated in arrests in Denver are analyzed at the Denver police laboratory. Less than 10% of the drugs analyzed there are opiates. Approximately half are heroin and half are pharmaceuticals diverted from legal trade by robbery, fraud, or deceit. The quality of confiscated heroin has been declining during the past three years and is currently running from 1/2 to 1 1/2% per sample. The cost of a single balloon or bag of heroin is currently $25.00. Drugs confiscated outside of Denver are analyzed at the Colorado Bureau of Investigation laboratory. Opiates, primarily pharmaceuticals, form only a small proportion of the samples analyzed.

This research was partially supported by Grant number 5T32 DA 07043 from the U. S. Public Health Service.

An average of 347 people were receiving methadone at the three Denver clinics during the nine months covered in this study. ARTS, the largest of the three and the one linked to those arrested, averages 221 clients, of whom approximately 62% are treated with methadone. The remainder either abuse non-opiates or are drug free. Approximately 53% are Anglo, 28% Hispanic, and 16% black. The remainder are Native American or Oriental. The median age is 29, with a range of 20 to 60 years. Approximately 70% are males. The average dose of methadone is 34 mg.

Urine specimens are required once in every seven days from most of the clients who receive methadone or currently abuse non-opiates. Clients who have had no dirty urines for six months are only required to give urine specimens once each month. Additional specimens may be required at the discretion of the client's counselor. Urine specimens from the Denver methadone programs are analyzed at the Colorado Department of Health laboratory. They are routinely screened for the presence of morphine, dilaudid, codeine, demerol, oxycodone, and hydrocodone using a combined EMIT (Enzyme Multiple Immunoassay Technique, The CIVA Co.) and thin layer chromatography procedure developed at that laboratory (Wislocki et al. 1974).

FIGURE 1

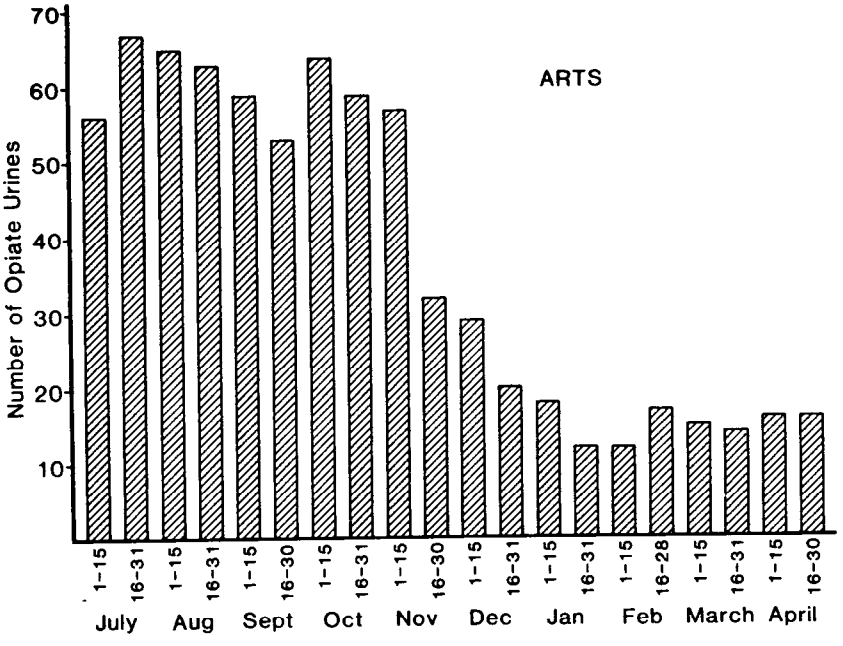

Figure 1. Number of opiate urine specimens collected at the ARTS clinic in 15-day periods before and after the November 10th police operation

The dramatic decrease in the number of urine samples with detected opiates collected at the ARTS clinic following the November drug bust is shown in Figure 1. The number of urines with detected opiates in the 18 weeks following the police operation was less than 1/3 that of the preceding 18 weeks. It is interesting to note that the highest point after the bust is lower than the lowest point before the bust. The percentage of methadone clients responsible for opiate urines is shown in Figure 2. It is clear in these two graphs that fewer clients were using opiates after the drug bust and those who were using, were using less often.

FIGURE 2

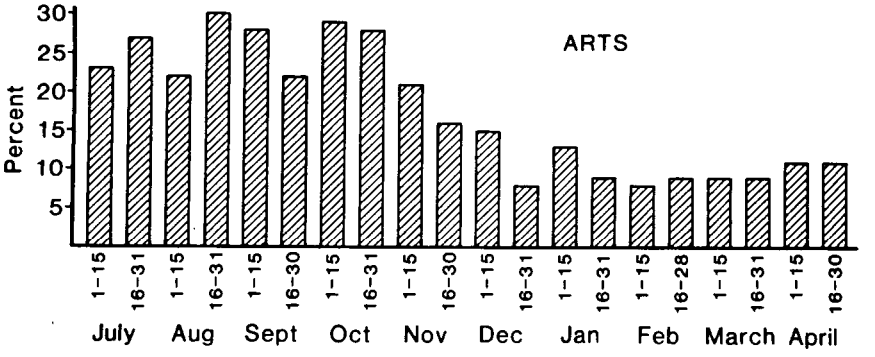

Figure 2. Percentage of clients responsible for opiate urines collected at the ARTS clinic shown in 15-day periods

The impact of the police action against drug dealers was clearly reflected by the decrease in opiate urine samples collected at the ARTS clinic. We hypothesized that the client population of another clinic which was not mentioned in the newspapers in connection with the drug bust, but which is within one half mile of the ARTS clinic, would have been similarly affected, but that the third clinic, located four miles west, would not have been affected. We assumed that demonstrating this difference would provide even stronger evidence of the efficacy of local law enforcement against pushers in a setting such as Denver's. An interservice agreement to allow examination of the urine data slips from the other two clinics was negotiated withthose clinics through the good offices of the Colorado Department of Health, Alcohol and Drug Abuse Division. Copies of the urine data slips contain only numbers and are filed at the state health laboratory. There was no way in which an urinalysis report could be associated with a name or other individual identification by the researcher, so there was no possibility of a breach of confidentiality. The agreement was cleared by the Division of Methadone Monitoring of the U.S. Public Health Service.

The population of the eastside clinic, near ARTS, is similar in composition to that of the ARTS clinic. Approximately 42% are

Anglo, 23% are black, and 32% are Hispanic. At the clinic on the west side of Denver 61% are Anglo, 4% are black, and 48% are Hispanic. The average methadone dose at both clinics is approximately 35 mg. Most clients are in the 20 - 35 year age range and 66% are males.

To our surprise, urine data from both of the other clinics showed the same steep decrease in detected opiates following the November police action. The combined data from all three clinics reflects the opiate drug use of essentially all of the opiate abusers in treatment in metropolitan Denver. The number of opiate urines collected in Denver 18 weeks before and 18 weeks after the November 10th police operation is presented in Figure 3. The percentage of methadone clients responsible for the opiate urines in the same period is shown in Figure 4. Again it is clear that, for the city as a whole, fewer clients were using opiates and those who were, were using them less often.

FIGURE 3

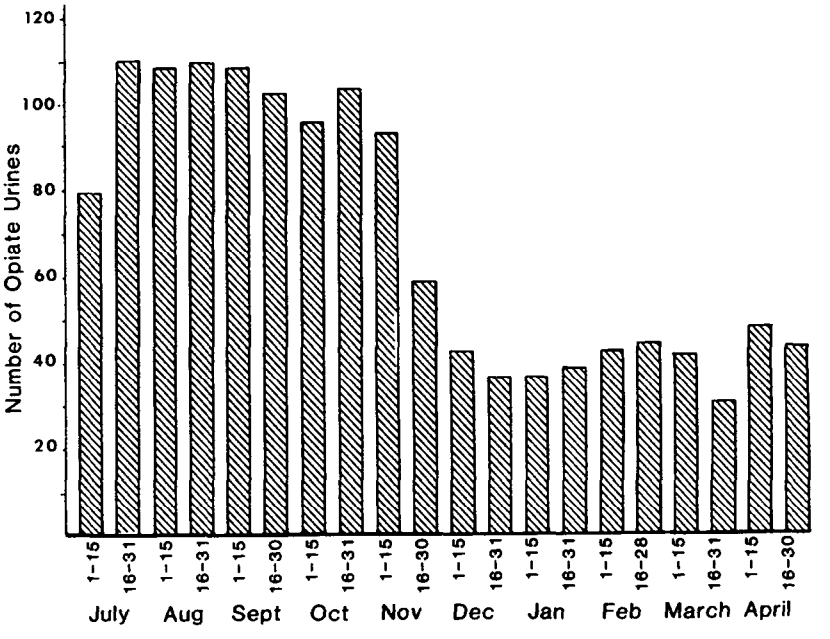

Figure 3. Number of urine specimens with opiates collected from the opiate abusers in methadone treatment programs in Denver before and after the November 10th police operation

FIGURE 4

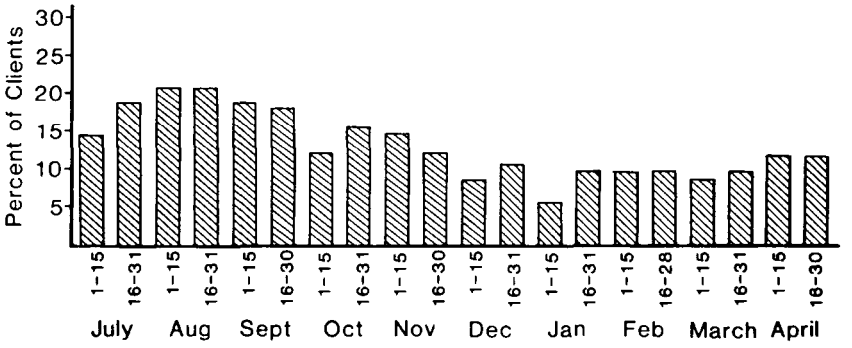

Figure 4. Percentage of clients in methadone programs in Denver responsible for opiate urines before and after the November 10th police operation

The urine data from the three clinics present a graphic example of the effect of heroin supply interdiction by the Denver police, but we were also interested in the clinical impact on individual clients. A sample of clients was drawn from the ARTS clinic using the artitrary criteria of opiate use in November with a minimum of two opiate urines in the preceding four months and two or less in the succeeding four months. Clinical records of the 21 clients who met these criteria were reviewed and their counselors interviewed. One of the 21 was deleted because the opiates he used had been prescribed for suitable medical reasons and verified. Of the remaining 20, four have successfully completed detoxification from methadone. One of these has left treatment and is reported by friends still in treatment to be doing well. The second maintains contact with the clinic and is doing well. Another developed a serious drinking problem, but is still receiving counseling and is described as improved. The fourth expressed concern about his drinking, but left treatment anyway. Six have shown improvement and are still in treatment. Of these, three requested increases in their methadone doses shortly after November 10th. Three clients, who were on high doses of methadone (50 - 60 mg.) and had been using heroin frequently, transfered to clinics on the east coast. Seven clients were discharged as treatment failures. One of the seven was jailed for obtaining narcotics by fraud while on probation on the same charge. The rest simply left the program while on moderate doses (20 - 30 mg.) of methadone. Nineteen of the 20 subjects had illegal non-opiate drugs detected in their urine samples after November 10th.

A striking aspect of the clinical information is that clinic personnel were unaware of the radical change in opiate use before these data were compiled, and there is no mention of the bust or its effect on individual clients in the 21 surveyed charts, with the exception of the two who were arrested. Even in those two

cases the change in the patterns of drug use was not noted. Anecdotal reports from the other two clinics in Denver indicated that the counselors there were also unaware of the change, and some counselors thought that opiate use might have been increasing in the first four months of 1980.

There are several possible reasons for the counselors' unawareness of the pattern of opiate use within the clinics. The heroin available in Denver is of poor quality and has been in short supply in recent years. The majority of clients using illegal opiates were not using them on a daily basis, so cutting off the the supply did not have a drastic effect on their lives. Most of the clients who were using heroin also abused other drugs, particularly benzodiazepines, which probably lessened the impact of the reduced heroin supply and obscured the change in opiate use from the counselors' views. The determining factor may have been that the urinalysis data come to the counselors in batches several times each week and are difficult to comprehend in this fragmented form.

The majority of the clients in this population have significant emotional, interpersonal, and employment problems, which tend to be the focus of clinical intervention. This emphasis is based on the assumption that resolving these issues will enable clients to alter their drug use successively during the course of treatment. On the other hand, drug use impedes clients' progress in improving their life situations. It may well be that greater emphasis on reducing drug use concomitant to resolving emotional, social, and employment problems would be a more effective approach. Urinalyses are the best evidence of clients' drug use available to the drug counselor. They provide a valid and reliable check on the clients' reports of their drug use and can be used in conjunction with the clinical interview to clarify the pattern and circumstances of clients' drug use. Clarification can, in turn, facilitate the development of strategies to help the client avoid drug use in the future.

Supply interdiction is an expensive operation for the police, entailing, as it does, months of undercover work and the expenditure of cash for drug purchases by agents. But the success of such action in reducing the quantity of drugs available to abusers in a situation of relative isolation like Denver's is clearly demonstrated by the data presented here. Hopefully, recognition of the efficacy of law enforcement efforts will lead to more rigorous action against non-opiate dealers as well as heroin dealers in the future.

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Narcotic Addiction: A Changing Scene?

D. N. Nurco, I. H. Cisin, and M. B. Baiter

INTRODUCTION

The purpose of this paper is to explore changes in the narcotic addiction[1] scene in an era of rapid social change. The quarter of a century covered by this study embraces an era in which major significant changes have occurred in this society.

The Sample and Data

A sample of 499 subjects was selected from a roster of male narcotic abusers first known to the Baltimore City Police Department Narcotic Squad between the years 1952-1976, inclusive. From each year's contribution to the roster, ten whites[2] and ten blacks were selected in a random, stratified manner, and 402 were interviewed. The data to be analyzed were drawn from a structured interview schedule devised by the project staff; each interview took approximately three hours and was administered by a staff member especially trained for this purpose.

In this report, the data[3] have been weighted to compensate for differential sampling by year of entry onto the roster, so that the total for the population and the totals for various groupings correctly reflect population parameters.

Although the selection of subjects was based on year of entry onto the police roster, the information available from the interviews permitted: (1) confirmation of addiction status; and (2) reclassification of addicts into incidence cohorts, defined in terms of the year of onset of narcotic addiction. The present report is confined to those incidence cohorts for which at least ten years of data were available from time of onset of addiction to time of interview. The choice of a ten-year period was felt to provide sufficient sensitivity to any fluctuation (or lack of fluctuation) in the behavior of narcotic addicts. A total of 238 narcotic addicts (103 whites and 135 blacks) qualified for analysis in this manner.

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* This paper is a brief summary of two longer works, entitled "Addict Careers: I. A New Typology" and "Addict Careers: III. Trends Across Time," which will be published in EINSTEIN: The International Journal of the Addictions, Volume 16, 1981, by MARCEL DEKKER, INC.

The incidence cohorts constructed for this report reflect the trends across time of the characteristics of new recruits into narcotic addiction. For simplicity, the incidence cohorts have been grouped into three: pre 1955 (1937-1954); 1955-59; and post 1959 (1960-1966).

TRENDS IN CHARACTERISTICS OF NARCOTIC ADDICTS

Race

The data of the current study, based on and projected to a roster of all addicts known to the police of Baltimore City over a quarter of a century, confirm the predominance of blacks in the addict population. Indeed, when the data are classified according to the onset of addiction, there is only minor fluctuation in the black-white ratio over time. During the years 1955-59, there seems to have been at least a slight increase in white representation among addicts, but subsequent years showed a slight decline in the white proportion. Thus, it is appropriate to say that for every ten men entering addiction at any given time, seven or eight were likely to be black.

Because of the racial imbalance of the addict population known to the police, the tables in this report, based on sample weighted to provide projections to the addict population, are presented separately for black addicts and white addicts.

Background Characteristics

Although the numbers drawn into the addict population varied considerably across time, it appears that the appeal of addiction was essentially to the same population groups during all the periods studied. There were differences between the background characteristics of blacks and those of whites who were attracted into addiction, but within each racial group of addicts separately, there was little variation in such characteristics across time.

Among the whites in all three periods studied, the median social status of new addicts fell in the semi-skilled, blue-collar class; median educational attainment in all three periods involved drop-out at the junior high school level. Social stability (as reflected by years of longest residence before finishing high school or leaving school) showed considerable dispersion among individuals in all three time periods.)

Among the black addicts, the picture was essentially the same: no clear trend in the social status of those attracted to addiction (although the black addicts were consistently drawn from a lower social class than the whites); a consistent picture of early drop-out from school; and no clear trend in social stability.

For both races, the persons who entered addiction later in the quarter century studied were more likely than those who became

addicted earlier to have had contacts with juvenile authorities and to have had acknowledged criminal activity prior to first narcotic use.

INTRODUCTION TO NARCOTIC USE

In the pre-1955 period, the median age of onset of addiction for white addicts was just over 18 years; for black addicts, it was more than a year older. During the 1955-59 period, the onset of addiction occurred more than a year and a half earlier on the average; but after 1959, the trend was reversed so that new addicts, both white and black, showed a median age of onset of 18.0 years.

Not all narcotic addicts are always addicted to heroin. It would appear that the ready availability of liquid codeine during the 1955-59 period proved remarkably attractive, particularly to white, addicts. Indeed, among white addicts, liquid codeine was the drug of choice for the majority of new addicts recruited between 1955-59. After 1959 liquid codeine and other narcotics became less readily available (Nurco et al. 1979) and the pattern of drug choice among white addicts reverted to emphasis on heroin. Among black addicts, although liquid codeine became considerably more popular beginning in 1955, its popularity never seriously threatened the predominant position occupied by heroin.

TRENDS IN NARCOTIC ADDICT CAREERS

All of the addicts in the sample used for this report provided data covering a ten-year career beginning with the onset of addiction. Thus it was possible to describe their entrances and exits to the addict population and their activities during that ten-year period, even if only a small part of the ten years involved active addiction.

In order to study these ten-year careers in an orderly and systematic manner, a typology was constructed around two fundamental concepts: 1) commitment to addiction, as reflected in the proportion of the ten-year period spent actively addicted; and 2) voluntary abstinence, as reflected by the relative allocation of time to nonaddictive periods in the community and to periods of time spent incarcerated.

The typology of addict careers presented here is built upon the concepts of opportunity and motivation to use drugs, i.e., characterization depends upon degree of involvement with narcotic drugs in relation to opportunity for voluntary abstinence. This typology takes into account the time spent in each of the following statuses:

1. Addicted;
2. In the community, not addicted;
3. Incarcerated.

Emphasis is on the degree of involvement with narcotic addictive drugs, on opportunity to use such drugs as represented by time in the community as opposed to jail, and on voluntary abstinence,

Degree of involvement is defined as the proportion of the total available time (10 years) during which the subject was addicted. Opportunity to use drugs is defined as the proportion of the base period (10 years) in which the addict was living in the community (as contrasted with being incarcerated)--whether using drugs or not. Voluntary abstinence is defined as the proportion of the period (10 years) in which the addict was living in the community but was not addicted. This formulation assumes that the two variables (opportunity and involvement) are independent at any level of involvement less than 100 per cent. The independent contribution of opportunity becomes more apparent at middle or lower ranges of involvement, where issues of choice become paramount.

Application of these concepts to the data of the present study yields five clearly distinguishable types:

Type I. Low involvement with narcotic drugs as displayed by those who used narcotics on a "daily basis" less than 50 per cent of the time, i.e., less than an aggregate of five years out of the ten; high opportunity in that they spent no more than two and one-half years incarcerated; and high voluntary abstinence as demonstrated by the fact that they were in the community at least seven and one-half years and chose to be addicted only a relatively small proportion of this time.

Type II. Low involvement (used narcotics less than an aggregate of five years); low opportunity in that they spent more than two and one-half years incarcerated; and low voluntary abstinence in that they had relatively little drug free time in the community.

Type III. Medium involvement, with 50-74 per cent of the ten years devoted to the addiction; high opportunity, since not more than two and one-half years of the remaining time was spent incarcerated; and a median level of voluntary abstinence.

Type IV. Medium involvement, with 50-74 per cent of the total period devoted to addiction; low to medium opportunity, since more than two and one-half years were spent incarcerated; and, therefore, little remaining time for voluntary abstinence.

Type V. Highest involvement, with at least seven and one-half of the ten years devoted to addiction; therefore, it follows that opportunity was high and voluntary abstinence was low.

Figure I displays characteristic patterns of movement among the statuses ON, OFF in the community, and INCARCERATED for the five types described above. Although it is recognized that no single case can adequately represent each type because there is considerable variation among the members, the five typical cases presented in Figure I convey the fundamental characteristics and

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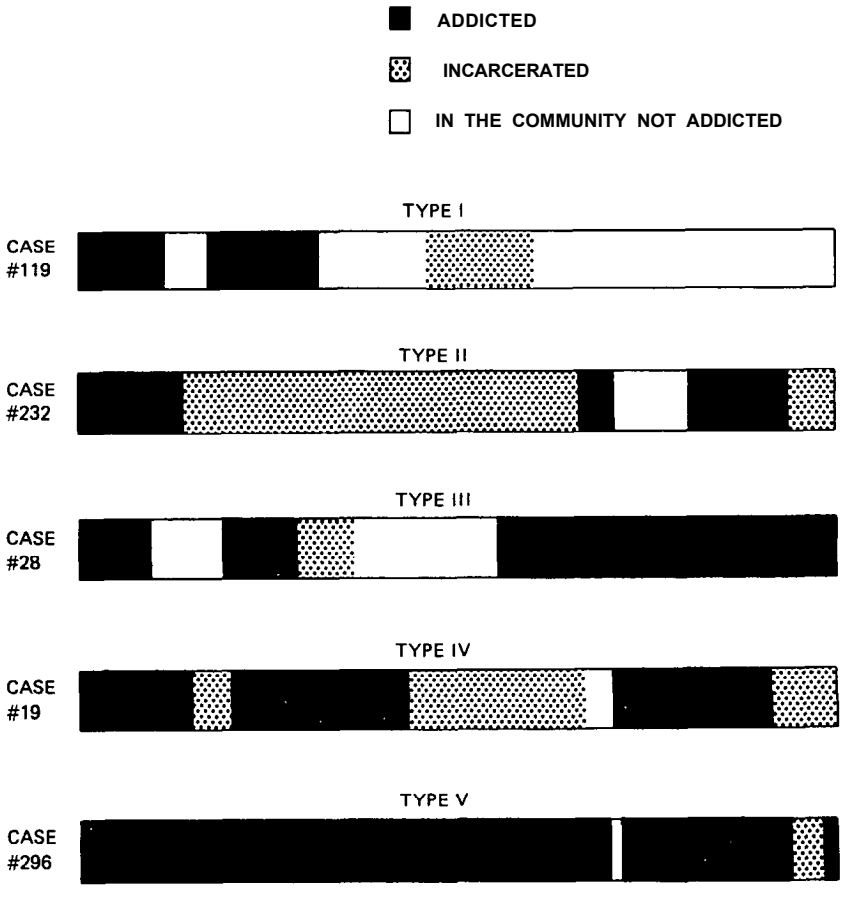
FIGURE 1

CHARACTERISTIC ADDICT CAREERS: THE FIRST TEN YEARS

ALLOCATION OF TIME TO THREE ACTIVITIES



differences among the types in the total ten-year developmental patterns.

Using this typology to characterize the ten-year careers, what can be said about trends across time? In other words, what effect do the ambient conditions related to the starting date of a career have upon the nature of the career?

Certain characteristics of the addict's careers seem to be reasonably stable across time. For example, among black addicts, the modal career during all time periods is best described as Type V: virtually uninterrupted addiction during a ten-year period, with little or no incarceration. This single type characterized 44 per cent of the black addicts who began their careers before 1955, more than half of those who began during 1955-59, and over one-third of those in the subsequent time period.

Among the white addicts, the distribution of career patterns showed a much less pronounced tendency toward uniformity. In the pre-1955 period and in the post-1959 period, approximately one-third of the white addicts displayed a Type I pattern in their ten-year careers, i.e., they exercised maximum control over their habits, with a great deal of time abstinent in the community. During the 1955-59 period, the popularity of this type of pattern declined somewhat.

Some of the trends across time were clearly monotonic. Among blacks, the popularity of Type III and Type IV patterns increased steadily across the time periods studied. Among whites, Type II patterns became considerably more frequent as time went by; concomitantly, Type IV patterns went steadily downward in relative frequency. This latter finding suggests that among whites, the pattern of "confirmed junkie" (Type IV, with much time spent in addiction, much of the remainder spent incarcerated) was being replaced by a pattern (Type II) in which less time was spent in addiction and more time incarcerated.

The remaining career patterns showed quite irregular trends across time. Among the black addicts, the popularity of Type I and Type II careers declined in the 1955-59 period and then increased in the direction of pre-1955 levels. Among whites, Types I and III showed this same tendency to decline between 1955-59 and then to revert. The white Type V'S became more frequent during the 1955-59 period (just as the black Type V's did) and then subsequently declined in popularity.

In an earlier discussion of career patterns (Nurco et al. 1978), it was noted that the ready availability of narcotics other than heroin (particulary liquid codeine) had a marked effect on the patterning of the habit among white addicts. This fact is dramatically illustrated by an analysis of the popularity of heroin during the ten-year careers. The dominance of heroin was determined for each addict by calculating what proportion of months of addiction were characterized as heroin-dominated. For black addicts,

there was not very much variation across time, although there was some noticeable tendency for heroin to be less dominant during the 1955-59 period. For white addicts, on the other hand, the picture was completely different. Whites who joined the addict population prior to 1960 showed a very strong tendency to regard some drug other than heroin as their dominant drug. After that time, when liquid codeine became much more difficult to obtain, the pattern of drug dominance for whites became indistinguishable from that for blacks, with heroin being overwhelmingly dominant.

To what extent have criminal activities of addicts changed across time? As a partial answer to this question, we have summarized, for the three cohorts under discussion, the proportion of their income that came from illegal sources during their ten-year careers. The trend shows a slight decline in the importance of illegal income when one compares the addicts who began their careers in 1955-59 with those who began earlier, followed by a noticeable increase among those who began their careers in 1960 and thereafter. In the final cohort, on the average, about three-fourths of each addict's income (for both black and white addicts) was derived from illegal sources.

FOOTNOTES

1. Narcotic addicts are defined in this study as persons who have used opium, its derivatives, or synthetics for non-medical reasons four or more days a week for at least a month. Onset of addiction was defined in terms of the first occurrence of such a period.
2. Only nine whites were available in 1956.
3. All appropriate tables have been deleted from this abbreviated presentation and appear in the International Journal of the Addictions, Vol. 16, 6 & 8.

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Relative Analgesic Potency of Intramuscular Heroin and Morphine in Cancer Patients With Postoperative Pain and Chronic Pain Due to Cancer

R. F. Kaiko, S. L. Wallenstein, A. Rogers, P. Grabinski, and R. W. Houde

Heroin has been judged to produce more euphoria and less side effects than morphine (Seevers and Pfeiffer 1936; Ross 1944; Elliot et al. 1971) and has been used in some countries in controlling pain in patients with advanced cancer (Twycross 1974; Twycross 1975). While controlled comparisons of intramuscular heroin and morphine have been carried out in postoperative patients (Reichle et al. 1962), such assays have not been carried out in patients with chronic pain due to cancer. Apart from differences in potency and time action, heroin has been found to be similar to morphine in most respects, so that the uniqueness of heroin's attributes has been questioned (Lasagna et al. 1955; Fraser et al. 1961; Martin and Fraser 1961; Smith and Beecher 1962; Reichle et al. 1962).

The studies reported here are intended to provide estimates of relative analgesic potency and more substantial information as to whether heroin has any unique attributes in the treatment of cancer patients with postoperative pain and pain due to advanced disease. The purpose of the initial study was to determine the relative analgesic potency of heroin and morphine and to compare side effects and alterations in various elements of mood of equianalgesic doses of the two drugs in patients with postoperative pain. In addition, the concurrent use of categorical (CAT) pain and pain relief scores with visual analog scales (VAS) was employed for the purpose of providing infomation as to their relative merits in assays of analgesic drugs. Preliminary results are also reported for two additional, but yet incomplete, studies in patients with chronic pain due to advanced cancer. The first of these studies is intended to provide potency estimates and to compare side effects and mood changes at equianalgesic doses of heroin and morphine. The second study in patients with chronic pain is intended to provide estimates of relative potency of oral as compared to intramuscularly administered heroin.

METHODS

Intramuscular doses of heroin hydrochloride of 2 and 4 mg were compared with 8 and 16 mg of morphine sulfate in one series and 4 and 8 mg of heroin compared with 8 and 16 mg of morphine in a second series of double blind, twin crossover relative analgesic potency assays in patients with postoperative pain. In a second study, intramuscular doses of heroin of 4 and 8 mg being compared with 8 and 16 mg of morphine in a complete crossover assay; and in a third study, intramcular heroin, 4 and 8 mg, is being compared to 10 and 20 mg of oral heroin in one series and 20 and 40 mg of oral heroin in another series of complete crossover assays in cancer patients with chronic pain due to advanced disease.

The method and design of the assays have been previously described in detail (Houde et al. 1960; Wallenstein and Houde 1975). The methods and modifications employed in these particular studies are briefly described below. Each twin crossover assay consists of a series of four treatment studies incorporating a lower and upper dose of the standard and test drug. The ratio of doses of standard to test drug is varied from study to study. Each patient receives two doses, a lower dose of one drug and an upper dose of the other. Each block of four patients is balanced for drug, dose and order, and the assignment of patients to treatments within the block is randomized. On completion of each block, a sequential decision-making process is instituted to determine whether the next block should incorporate a lower or higher ratio of standard to test drug. The objective of the process is to obtain as much data as possible in the equianalgesic effect range of the two drugs. In the complete crossover assay, each patient receives each of the four study medications according to a series of randomly chosen Latin squares.

Patients are selected on the bases of an evaluation of the cause of pain, the appropriateness of treatment with the study drugs and the ability of the patient to communicate with the observer. Patients are seen at hourly intervals and questioned about the severity of their pains. If the patient requests medication for pain and has not received an analgesic for at least three hours, and if the pain is reported as moderate or severe, a study drug is given by the nurse observer. Observations are then made at one half hour and at one hour and continued at hourly intervals for six hours or until pain has returned to the premeditation level. At each observation time, the patient is questioned as to the severity of pain and the degree of pain relief according to the standard CAT pain and pain relief scores, whether or not the pain has been at least half relieved and whether or not the patient considers the drug acceptable. Volunteered and observed side effects are also recorded.

Patients are also asked to complete VAS and word-pair questionnaires. VAS data are obtained at the same observation times as CAT data. The patient is asked to mark 100-millimeter scales at the point on the line which best reflects how he feels between "Worst I Could Feel" and "Best I Could Feel" for the mod VAS,

"Least Possible Pain" and 'Worst Possible Pain" for pain VAS and "No Relief of Pain" and "Complete Relief of Pain" for relief VAS. The millimeter distance from the origin to the mark is measured and taken as the VAS score. At the time of drug administration and at 2 hours after drug, patients are also requested to estimate various elements of mod by use of a set of 15 contrasting word-pairs (Lasagna et al. 1955). Patients are instructed to circle either a neutral, "0", point or a "1", "2" or "3" in the direction of either word of the pair. Negative feelings are later assigned negative signs and positive feelings, positive signs. The number is taken as the mod questionnaire score for each pair of words.

RESULTS AND DISCUSSION

Postoperative pain

The mean age of the study population was 50 years with a range from 19 to 72 years. One hundred of the patients were male and 66 were female. The site of pain was predominantly abdominal or thoracic. Study drug was usually administered during the day after surgery and the following day. Meperidine and levorphanol were the most common routine postoperative narcotic analgesics. One hundred and twenty-four patients completed the assay. This included 32 patients in the lower heroin (2 and 4 mg) series and 92 patients in the higher (4 and 8 mg) series.

Analyses of variance for twin crossover assays were carried out with modifications for sequential study design (Finney 1964). The relative analgesic potency data derived from CAT pain (SPID, sum of pain intensity differences; PPID, peak pain intensity difference) and pain relief (TOTPAR, total pain relief; PPR, peak pain relief) scores are summarized below.

Table 1. Relative Analgesic Potency of Intrarmuscular Heroine vs. Morphine in Cancer Patients with Postoperative Pain (N, 124)

Analgesic Parameter	Relative Potency	95%C.I.	Lambda	Heroin HCl mg Equivalence to 10 mg Morphine Sulfate (95%C.I.)
TOTPAR	1.9	1.4-2.4	0.44	5.3 (4.1-7.3)
PPR	2.2	1.4-3.1	0.60	4.6 (3.2-7.2)
SPID	1.5	0.7-2.3	0.67	6.5 (4.4-14)
PPID	2.0	1.2-3.1	0.67	4.9 (3.3-8.6)

Relative potency estimates based on peak effects were higher than those based on total effects, an indication that heroin has a shorter duration of action than morphine at equianalgesic peak effects. The use of pain relief data provided more efficient estimates of relative potency than the use of pain intensity data. The data show that approximately 5 mg of heroin and 10 mg of morphine are equianagesic in relieving postoperative pain.

The concurrent use of CAT and VAS scores allowed a comparison in terns of the statistics generated in the estimation of relative potency. The use of VAS data provided estimates of relative

analgesic potency comparable to those provided by the use of CAT data, but VAS data provided estimates which were more efficient (lower lambda) and which had consistently narrower confidence intervals. These differences may result from the fact that VAS allow the patient to make finer distinctions than CAT scores.

Side effect occurrence after heroin and morphine was dose related and within a comparable range (table 2). The most common effects (sleepy, relaxed, dry mouth, groggy, lightheaded, dizzy, nausea, sweating and weak) were of the highest incidence for both drugs. The number of particular types of effects exclusive to heroin outranked those exclusive to morphine (20 vs. 7), but these particular effects had a very low incidence.

Table 2. Side Effect Occurrence after Intramuscular Heroin and Morphine in Cancer Patients with Postoperative Pain

	Heroin			Morphine	
Dose.....	2 mg	4 mg	8 mg	8 mg	16 mg
N(patients, meds.)....	18	69	60	73	71
Pts. with side effects.	10	44	44	40	53
% with side effects....	56	64	73	55	75

The use of a global VAS mod measurement and the word-pairs allowed for comparisons of mod effects at equianalgesic effects of heroin and morphine. No significant differences were observed in the mean peak VAS mood scores after heroin as compared to morphine at any level of CAT peak pain relief. Generally, higher mod scores were associated with greater pain relief. The results of the word-pair questionnaire (table 3) in terms of the differences between the 2 and 0 hour scores demonstrate that both drugs provide significantly improved mod. There was a trend, however, for heroin to provide a smaller increase in scores as compared to morphine at a comparable decrease in pain intensity. These results must interpreted in view of the fact that patients were dosed according to the severity of their pain rather than according to the nature of their mood. Patients who initially report relatively low mood scores report positive changes after drug, whereas those patients who initially report high scores report small or negative changes following drug (Kaiko et al. 1980).

Chronic Pain

Significantly less pain relief and lower mood scores were observed in patients with chronic pain as compared to patients with postoperative pain, indications that patients with chronic-pain are more tolerant to the effects of both drugs. In addition, prestudy drug word-pair scores demonstrate significant differences in various elements of mod as compared to scores in postoperative patients.

Thirty-six patients with chronic pain have, thus far, completed the graded dose comparison of heroin and morphine. This study remains in progress, but preliminary results are consistent with

Table 3. Differences between 2 and 0 Hour Word-Pair Scores after Intramuscular Heroin and Morphine in Cancer patients With Post-operative Pain

	Heroin, 4.8 mg (N, 110)			Morphine, 11.4 mg (N, 104)		
Word-Pair	Mean	SE	P<	Mean	SE	P<
Shaky-Serene.....	0.69	0.19	0.001	1.31	0.21	0.001
Restless-Peaceful.....	0.89	0.20	0.001	1.36	0.22	0.001
Uneasy-At ease.....	0.99	0.20	0.001	1.16	0.23	0.001
Nervous-Calm.....	0.63	0.19	0.005	1.01	0.19	0.001
Blue-Cheerful.....	0.64	0.15	0.001	0.67	0.17	0.001
Angry-Contented.....	0.30	0.15	0.05	0.42	0.13	0.005
sad-Happy.....	0.59	0.16	0.061	0.68	0.17	0.001
Alone-Sociable	0.23	0.22	0.3	0.56	0.21	0.01
Don't care-Interested..	0.39	0.18	0.05	0.11	0.19	0.6
Pessimistic-Optimistic.	0.17	0.16	0.3	0.26	0.15	0.1
Apprehensive-Confident.	0.35	0.19	0.1	0.64	0.16	0.001
Apathetic-Enthusiastic.	0.24	0.18	0.2	0.57	0.18	0.065
Heavy-Bouyant.....	0.51	0.15	0.001	0.55	0.18	0.005
Lethargic-Peppy.....	0.21	0.13	0.2	0.09	0.16	0.6
Serious-Amused.....	0.01	0.16	0.98	0.40	0.16	0.02
[Pain Intensity (VAS)..	-27	2.7	0.001	-29	4.6	0.0011

those obtained in postoperative patients. Estimates of relative analgesic potency are comparable to those obtained in postoperative pain and at a slightly sooner, equianalgesic peak effect, heroin appears to have a slightly shorter duration of action. The most common side effects axe shared by both drugs and no significant differences are being observed in peak VAS mood scores following heroin as compared to morphine at any degree of CAT peak pain relief. Changes in word-pair scores between 0 and 2 hours are, generally, not statistically significant, but changes after heroin are consistently smaller and primarily negative. The observation is consistent, however, with the smaller decrease in pain intensity at 2 hours after heroin as compared to after morphine.

Ten patients have, thus far, completed the comparison of intramuscular and oral heroin. This data indicates that equianalgesic peak effects are not being obtained With the intramuscular to oral dose ratios of 1/2.5 and 1/5. Although the data is too limited to provide valid estimates of relative potency, preliminary calculations suggest that approximately 30 mg of oral heroin is equivalent to 5 mg of intramuscular drug in terms of total pain relief and that a considerably higher oral dose would be required to obtain equianalgesic peak effects. A series incorporating an intramuscular to oral dose ratio of 1/10 has been initiated. These preliminary observations are in close agreement With the relative analgesic potency of oral as compared to intramuscular morphine (Houde et al. 1965).

SUMMARY

Heroin hydrochloride is approximately twice as potent as morphine sulfate, and acts slightly faster but for a shorter duration than morphine. Although patients With chronic pain due to advanced cancer differ from cancer patients with postoperative pain in terms of their degree of tolerance to the analgesic effects of morphine and heroin and their reports of various elements of mod, there is, thus far, no indication that heroin has any unique advantage over morphine in term of side effect occurrence or effects on mod at equianalgesic doses. Both drugs improve mod provided they are administered in doses which result in analgesia. While there appears to be some slight difference in the spectrum of side effects observed after heroin as compared to morphine, heroin and morphine share the most common side effects. The incidence of side effects following both drugs appear to be highest among those effects which are primarily somatic and undesirable. The use of visual analog scales concurrent With categorical pain and pain relief scores provides a means for the finer estimation of relative analgesic potency and time action.

The results of these studies are in general agreement with those of other investigators. Where apparent differences exist they can usually be explained on the bases of differences in methods and subject populations.

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ACKNOWLEDGEMENTS

This Work is supported in part by NIDA Grant No. DA-01707, NIA Grant No. AG-01441 and by NCI Core Grant No. CA-08748.

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Human Preference Comparison of Pentobarbital, Diazepam, and Placebo

R. R. Griffiths, G. E. Bigelow, and I. Liebson

Increasingly, human experimental methods are being developed to compare drugs with respect to their efficacy in maintaining drug self-administration behavior (cf Griffiths et al. 1980). The studies that have been conducted to date suggest that measures of the amount of drug self-administration behavior (Schuster et al. 1971; Griffiths et al. 1979; Bigelow et al. in press) and behavioral preference measures (Pickens et al. 1977; Johanson and Uhlenhuth 1978) provide infomation about the relative reinforcing properties of drugs. In one recent study (Griffiths et al. 1979) volunteers with histories of sedative drug abuse were permitted to self-administer orally under double-blind conditions several doses of pentobarbital, diazepam and chloropromazine for periods up to 15 consecutive days. Although all three drugs produced subjective effects and observable signs of sedative intoxication, the drugs were associated with different amounts of self-administration. Chlorpromazine was similar to placebo in that it did not maintain much self-administration. Both pentobarbital and diazepam did maintain self-administration with the higher dose of each associated with higher average levels (ingestions/session) than the lower dose. The high dose of pentobarbital was associated with higher average levels and more regular self-administration than was the high dose of diazepam.

The present double-blind preference comparison of pentobarbital, diazepam and placebo had several interrelated objectives. First, the study sought to provide more comparative information about the relative reinforcing properties, behavioral effects and subjective effects of pentobarbital and diazepam. Second, the study was undertaken to examine a totally different measure of drug self-administration behavior: drug preference. A previous study (Griffiths et al. 1979) had shown that pentobarbital maintained higher levels of self-administration than diazepam, and it was of interest to determine whether a drug preference measure would provide similar information about the relative reinforcing properties of these drugs. Such comparisons are

important to determining both the relative sensitivity of the behavioral measures and the generality of the observed results. Third, the present study was designed to permit repeated evaluation of subjective measures of drug effect (e.g., a subject completed drug liking scale) such that it was possible to examine the relationship between the subjective measures and the behavioral preference self-administration measure. This comparison is particularly interesting because it provides information about the commonly held assumption that subjective measures such as drug "liking" should covary with measures of drug taking.

METHOD

Subjects. Six male volunteers with documented histories of sedative drug abuse participated. On the basis of physical examination, history, routine laboratory chemistries and chest X-ray, participants were found to be without significant medical or psychiatric disturbance other than their drug abuse. All of the subjects had histories of abusing both barbiturates and benzodiazepines. Most subjects reported sporadic (as opposed to chronic) abuse of high doses of sedative drugs within several weeks to a month of admission to the research ward.

General procedures. Subjects participated while residing on an 8-bed behavioral pharmacology research ward. Following admission to the research ward subjects were observed for a three to seven day period prior to the initiation of the experiment; no subject showed any clear evidence of clinically significant physical dependence on sedative drugs as determined by gross clinical observation and routine monitoring of vital signs. Prior to research participation subjects were informed that various drugs would be available for self-administration during the study, and that these could include the major and minor tranquilizers, sedatives, stimulants and placebo. Other than this general information subjects were blind to the type of drug to be administered.

Daily experimental procedures. Days on which drug administration was scheduled alternated with drug-free days throughout the experiment. On drug days subjects were awakened by 8:00 a.m.; they were permitted to drink fruit juice or coffee in the morning, but were not permitted to consume milk or any solid food until 12:00 noon. On drug days a single oral dose of drug was dispensed at 11:00 a.m. according to procedures described Below. Drugs were administered and evaluated according to double-blind procedures; neither the subjects nor the staff who dispensed drugs and rated drug effects knew the identity of test compounds. For each subject, placebo, 400 mg pentobarbital and 200 mg diazepam were given an arbitrary letter code (e.g., A, B, C); codes differed between subjects. On some days (no-choice trials) a single letter coded compound was scheduled for administration and the subject was informed of the letter code prior to administration. On other days (choice trials) two coded compounds were

available for administration. Staff informed the subject of the two letter codes and the subject chose which compound would be administered. Starting at 1:00 p.m. subjects filled out four short questionnaires, including a drug-effect scale, a drug-liking scale, the Profile of Mood States (POMS; McNair et al. 1971), and a short form of the Addiction Research Center Inventory (ARCI; Martin et al. 1971). Also at 1:00 p.m. staff completed an observer-rated drug-effect questionnaire. At 3:00 p.m. and 5:00 p.m. subjects repeated the drug-effect questionnaire and the drug-liking questionnaire, and the staff repeated the drug-effect questionnaire.

Sequencing of drug exposure. Before beginning the experiment all subjects were initially exposed to 100 mg diazepam. The rationale for scheduling this initial dose was based on a clinical impression that developed during earlier research, that the effects of initial exposure to diazepam depended on the recency of prior use. More specifically, in previous research it seemed that there was substantial variability across subjects in the magnitude of drug effect after initial exposure to diazepam, and it seemed that this variability was reduced with subsequent exposures to diazepam. After this initial exposure to diazepam, subjects were given three no-choice trials involving exposure to the three drug conditions in a random order [placebo (PL); pentobarbital 400 ng (PB400); diazepam 200 mg (DIA200)]; then subjects were given in a random order three choice trials involving the three Possible drug combinations (PL vs PB400; PL vs DIA200; PB400 vs DIA200); the remainder of the experiment involved simply alternating between the three randomly sequenced no-choice trials and the three randomly sequenced choice trials. The total number of experimental observations was determined by the duration of subject participation.

Drug dispensing procedures. Commercially available preparations of diazepam (Valium) and pentobarbital sodium (Nembutal) were prepared prior to the experimental sessions by crushing and mixing the drug with approximately 4-12 g unsweetened soft drink mix (Kool-Aid) and 3-10 mg quinine sulfate. Each drug ingestion was dispensed from a small medicine cup and nurses were instructed not to allow the subject to see the powdered drug.

RESULTS

Unsystematic clinical observation revealed that both 400 mg pentobarbital and 200 mg diazepam produced similar central nervous system signs typical of sedative drugs, including ataxia and sedation. Analyses of variance and post hoc *t*-tests were used to evaluate drug effects on observer and subject questionnaire responses. Compared with placebo, pentobarbital and diazepam both produced increases of similar magnitude in subject and observer ratings of magnitude of drug effect, and in subject rated liking of drug effect at 2 hours post administration. Analysis revealed that for most subjects these measures were significantly influenced by pharmacological condition, with the two active drug

conditions differing significantly from placebo but not differing significantly from one another. There was no consistent pattern of statistically significant effects of the active drugs relative to placebo or to one another on the scales of the ARCI and POMS. Analysis of the subject- and observer-ratings of magnitude of drug effect as a function of time (2 hours, 4 hours, or 6 hours after drug administration) revealed a similar time course of effects for the two active drugs, With the magnitude of drug effect declining toward placebo values over the 6-hour period.

The results from the choice trials for the six subjects were relatively consistent. Without exception, subjects chose pentobarbital over placebo, and diazepam over placebo on all occasions. In the pentobarbital vs diazepam comparisons, all six subjects preferred pentobarbital (400 mg) to diazepam (200 mg): three subjects chose pentobarbital exclusively while the remaining three subjects chose pentobarhital on 67 percent, 67 percent, and 75 percent of the choice trials. These choice results Were statistically significant (x_r^2 =12.00, $p<0.01$, Friedman analysis of variance for ranks); pentobarbital Was consistently preferred to diazepam, and both these drugs were consistently preferred to placebo.

DISCUSSION

In the present experiment, pentobarbital (400 mg) and diazepam (200 mg) produced drug-effect ratings of similar magnitude on the subject- and observer-rated drug effect questionnaires, While placebo produced negligible effects. Choice results for the six subjects were relatively consistent. Without exception, subjects chose pentobarbital over placebo and diazepam over placebo on all occasions; in the between-drug comparisons all six subjects preferred pentobarbital to diazepam.

The present experiment showed that pentobarbital is preferred to diazepam at doses of the two drugs that produce similar elevations in ratings of drug-effect and drug-liking. The credibility of this finding is enhanced by several sources of information that tend to confirm the general relationship that pentobarbital is a more efficacious reinforcer than diazepam. First, a previous inpatient human drug self-administration experiment has shown that pentobarbital maintains higher levels and more regular self-administration than diazepam (Griffiths et al. 1979). Second, studies with rhesus monkeys have shown that pentobarbital is more effective than diazepam in maintaining intravenous self-administration (Yanagita and Takahashi 1973). Third, clinicians familiar with drug abuse clients estimate that the "euphoria" produced by pentobarbital is higher than that produced by diazepam (Wesson and Smith 1977). Finally, epidemiological measures which are presumed to indicate drug abuse liability uniformly rank pentobarbital higher than diazepam (Jones 1977; Cooper 1977; Marks 1978). As a whole, these data suggest that the preference results observed may reflect a real difference in the reinforcing properties of pentobarbital and diazepam. This convergence of

data helps validation an drug self-administration methods and suggests that such methods my provide information about the relative reinforcing properties of different drugs.

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ACKNOWLEDGMENT

This research was supported by National Institute on Drug Abuse grants R01 DA-01022 and 5 K02 DA-00050.

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Psychophysical Profiles Differentiate Drugs of Abuse

R. D. Hienz and J. V. Brady

The effects produced by drugs of abuse on complex human perceptual processes have provided the focus for an expanding research literature over the past two decades (Hoffer & Osmond, 1967; Malitz & Kanzler, 1970). Opiates, barbiturates, and benzodiazepines all produce decrements in visual pattern recognition (Sambrooks et al., 1977; Ogle et al., 1976; Bartus & Johnson, 1977; Rothenberg et al., 1977) and critical flicker fusion (Malitz & Kanzler, 1970; Ogle et al., 1976), and hallucinogens reportedly impair both auditory and visual discrimination performances (Key, 1961; Elsmore, 1972; Ferraro & Grilly, 1973). For the most part, the contribution of changes in basic sensory functions to such effects has been difficult to determine since the procedural approaches have encompassed a range of performance processes which are not readily dissected or differentiated. Recent developments in the refinement of psychophysical measurement techniques with laboratory animals (Blough, 1966; Stebbins, 1970a), however, have provided methodologies of demonstrated reliability and sensitivity for quantitative assessment of such sensory changes (Blough, 1957; Hanson et al., 1964; Myers & Bernstein, 1965; Stebbins, 1970b).

The present report describes the effects of both stimulant and depressant drugs of abuse upon psychophysical functions in non-human primates. Specifically, different patterns of dose-dependent changes in absolute auditory and visual thresholds and behavioral reaction times are documented following administration of pentobarbital, diazepam, chlordiazepoxide, and d-methylamphetamine in laboratory baboons.

Four baboons (*Papio anubis*), tested in a double-walled sound-attenuating chamber (IAC 1201-A), were trained on a reaction time procedure (Moody, 1970; Pfingst et al., 1975a,b) to press and hold a lever until presentation of a sound burst or light flash signalled availability of food reward contingent upon lever release. During auditory testing, 16.0 kHz pure tones were delivered through an overhead wide-range acoustic driver located 20 cm above ear level. During visual testing, stimuli were

provided by a slide projector which focused a one-inch back-lighted circular white patch on the response panel at eye level through an aperture in an otherwise light-tight chamber wall. A dimly flashing red cue light became steady contiguous with a lever press and served as feedback for the lever holding response. At varying intervals (1.0 to 7.3 sec.) following initiation of the holding response, a test stimulus (1.5 sec duration) was presented. Release of the lever in the presence of the test stimulus defined a correct detection of the stimulus, and produced a food pellet reward, terminated the test stimulus, and initiated a 1-sec intertrial interval (ITI). Lever releases prior to test stimulus onset or following test stimulus offset reinstated the ITI without food delivery. Reappearance of the flashing red cue light following the 1-sec ITI signalled initiation of the next trial. Daily 2 to 2.5 hour experimental sessions included approximately 500 such discrete reaction time trials.

Auditory and visual thresholds were determined in separate sessions by randomly varying the intensity of the test stimuli from trial-to-trial in accordance with the method of constant stimuli, and examining detection frequencies at each intensity. For the auditory modality, four intensity levels 10 dB apart of a 16.0 kHz tone were used, with the lowest level set just below an animal's estimated threshold. To measure the false alarm, or "guessing" rate, a series of "catch" trials (i.e., no stimulus presented) were interspersed among the test trials. For the visual modality four intensity levels, 0.5 log density units apart, of the white light were used, with the lowest level set just below the animal's threshold. Again, "catch" trials with no light were programmed to occur intermittently. For both modalities the threshold was corrected for "guessing" by defining the threshold as that stimulus intensity producing a detection frequency halfway between the false alarm rate and the 100% detection point.

Reaction times were measured as elapsed time between signal onset and lever release. Reaction times to white light and the 16.0 kHz pure tone produced similar reaction time functions, although the auditory reaction times were approximately 100 msec faster than the visual reaction times. Since the drug effects on the reaction time measure were the same regardless of whether the reaction-time stimulus was white light or the 16.0 kHz pure tone, only reaction times to white light are presented.

Drugs were administered intramuscularly (i.m.) immediately before each experimental session, followed by 15 minutes of dark adaptation and 15 minutes of "warm-up" on the reaction time task before threshold determinations were begun. Saline control sessions requiring return-to-baseline performances occurred between drug sessions.

Figure 1 shows the dose-dependent effects of diazepam, pentobarbital, and d-methylamphetamine upon auditory and visual

thresholds and reaction time. All data points represent average changes in the indicated function for two animals, and are derived from 1-hour segments during peak drug action times (i.e., 1 to 2 hours after i.m. injection at the start of each experimental session). The total range of values obtained from saline control sessions is shown on the left in each graph. Consistent elevations in the visual threshold and reaction time were produced at doses greater than 1.0 mg/kg for diazepam, and greater than 3.2 mg/kg for pentobarbital. Diazepam had a similar effect upon the auditory threshold, but pentobarbital doses up to 17.0 mg/kg produced no such changes. d-Methylamphetamine over the dose range of 0.01 to 0.32 mg/kg produced no changes in either the auditory threshold or reaction time, though an elevation in the visual threshold was observed at the highest dose of 0.32 mg/kg. Higher doses of all three compounds produced disruption of performance. For diazepam and d-methylamphetamine the next quarter-log dose step (17.0 and 0.56 mg/kg, respectively) produced complete cessation of responding. For pentobarbital, the 17.0 mg/kg dose shown in Figure 1 produced prolonged pauses in performance in one animal, and at 32.0 mg/kg anesthetic-like effects were observed in both animals tested.

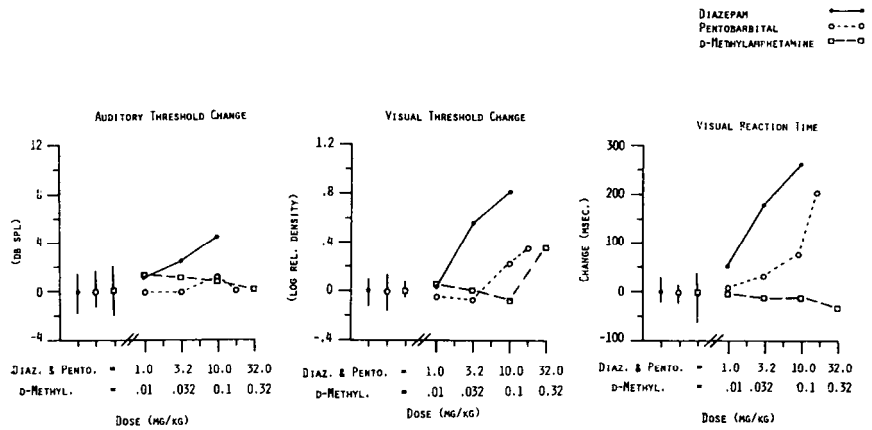

FIGURE 1 The effects of diazepam, pentobarbital, and d-methylamphetamine on auditory and visual thresholds, and reaction time

The consistent pattern of psychophysical change observed with pentobarbital (elevated visual thresholds but no auditory threshold elevation) has been systematically observed with one additional barbiturate, amobarbital, over the same dose range (1.0 to 17.0 mg/kg). Both the visual threshold and reaction time increased in a dose dependent fashion with significant elevations following doses of 10.0 mg/kg and 17.0 mg/kg. Over the same dose range, however, amobarbital did not produce any change in auditory

thresholds. In contrast, psychophysical determinations over the same dose range (1.0 to 17 mg/kg) with a second compound in the benzodiazepine class, chlordiazepoxide, revealed no changes in either the visual threshold, the auditory threshold, or reaction time. When chlordiazepoxide was administered at a dose beyond this comparative range (i.e., 32.0 mg/kg) in one animal, however, significant elevations in both the auditory threshold and reaction time were observed without any change in the visual threshold.

Confidence in the validity and reliability of the observed threshold shifts is based upon the following considerations. First, reaction time changes with the barbiturate compounds were observed during both auditory and visual modality determinations though auditory thresholds did not change. Secondly, calculated shifts in sensory threshold estimates due to drug-induced increases in reaction time were negligible compared to the magnitude of the observed threshold shifts. Finally, control studies have confirmed that auditory threshold shifts can occur in the absence of reaction time changes. Temporary acoustic threshold shifts induced by pre-exposure to 100 dB of broadband noise for 30-45 minutes elevated auditory thresholds by 15-20 dB. During this time of peak auditory threshold elevation, reaction times to the audible stimuli were within normal limits as were all visual reaction times. These observations indicate that the reaction time measure and the threshold measure can be considered to reflect independent functional changes to at least some degree.

The results of these experiments show clearly that drugs of abuse can be differentiated with respect to their effects on a range of psychophysical functions. Dose-dependent decrements in visual thresholds and reaction time in the absence of auditory threshold shifts were consistently observed within the class of barbiturate compounds studied. In contrast, the effects produced on these same psychophysical measures over a comparable dose range by representative benzodiazepines were differentiated both within and between drug classes. Diazepam elevated both auditory and visual thresholds and increased reaction time in a dose-dependent manner, while chlordiazepoxide over the same dose range (i.e., 1.0 to 17.0 mg/kg) produced no change in either auditory or visual thresholds or reaction time. Only at the highest doses beyond this range (i.e., 32.0 mg/kg) did chlordiazepoxide elevate the auditory threshold and reaction time without effect upon the visual threshold. Moreover, the unremarkable effects of the prototypical stimulant d-methylamphetamine, showing no change in auditory threshold or reaction time and an elevation in the visual threshold only at the highest dose administered (i.e., 0.32 mg/kg), clearly contrast with the psychophysical patterns observed with both the barbiturates and benzodiazepines.

These findings strongly suggest the need for a more extended analysis of the basic psychophysical effects of pharmacological agents to determine the extent to which such changes contribute to the sensory and behavioral dysfunctions associated with drugs of abuse.

SUMMARY

Behavioral reaction times and both auditory and visual absolute thresholds were determined in baboons before and after the administration of stimulant and depressant drugs of abuse. Pentobarbital and diazepam increased reaction times and elevated the visual threshold in a dose-dependent manner. Diazepam also raised the auditory threshold though pentobarbital did not. Chlordiazepoxide affected neither sensory thresholds nor reaction times over the same dose range; d-methylamphetamine elevated the visual threshold, but did not elevate the auditory threshold or increase reaction times.

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ACKNOWLEDGEMENTS

The research reported in this publication is supported in part by DEA Contract DEA78-9 and NIDA Grants DA-00018 and DA-02490

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Abuse Potential of Loperamide: Adaptation of Established Evaluative Methods to Volunteer Subjects

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For almost 30 years the assessment of the abuse potential of new opioid drugs on a depended unique collarboration between the pharmaceutical industry, the academic community and the Federal government's Addiction Research Center at Lexington, Kentucky. The Committee on Problems of Drug Dependance (at that time a part of the National Research Council and chaired, until his death, by Nathan Eddy) played a vital role in coordinating the movement of new products through the process of data acquisition and evaluation in both animals and man. The human testing involved the use of Federal prisoners with a history of opioid addiction who volunteered to be transferred from various Federal prisons to the Addiction Research Center. Because prisoner status required a controlled environment, research designs involving repeated measures could be undertaken with reasonable assurance that subjects were not simultaneously using nonprescribed drugs and, in most instances, that the dropout rate would be low. In 1975, after several years of discussion, Federal administrators accepted, for all practical purposes, the viewpoint that prisoners by virtue of being prisoners could not give a truly informed consent. The last prisoner left Lexington on December 31, 1976. The use of Federal prisoners was ended -- as was the program for assessment of abuse potential in humans.

The kinds of problems that might arise in attempting to carry out abuse potential assessments in non-prisoner volunteers were not clear. When drugs are abused, the dosage involved is often many fold greater than the recommended therapeutic doses. In order to test abuse potential before a drug is marketed, it is necessary to test various doses at levels that are pontentially toxic. Since by definition the drugs have not been released, there is no "street" experience to guide the investigator in determining the optimal dosage for testing or to advise an Institutional Review Review Board about expected toxicities or risks. In addition, it is necessary to assume that only a limited subgroup of the population may be vulnerable to an abuse potential. The best way to be certain that the drug is tested in vulnerable subjects is to test subjects with a pest history of opioid abuse or dependence. However, such subjects are not noted for their reliability in conforming to protocols. It was

to assess these administrative problems as much as to study the abuse potential of loperamide that we undertook the studies to be described.

Loperamide is a synthetic drug developed by Janssen Pharmaceuticals that is structurally related to diphenoxylate and to haloperidol. Studies in rats and mice suggested that it produced CNS actions only in doses many times higher than those required for anti-peristaltic actions and that, while it binds to opioid receptors in gut and brain, it appears to penetrate the CNS poorly (Colpaert et al. 1975; Terenius 1975). In studies at the University of Michigan and the Medical College of Virginia, parenteral loperamide (dissolved in propylene glycol) suppressed opioid withdrawal in monkeys and exhibited other opioid-like effects, but with oral loperamide it was difficult to establish clear-cut dose-response relationships (files of Janssen Pharmaceuticals). Subsequently, Yanagita and coworkers confirmed that loperamide produces opioid-like effects in monkeys and showed that monkeys would self-administer loperamide I.V. (Yanagita et al. 1980). On the basis of animal studies, parenteral loperamide would be expected to have some opioid-like abuse potential. However, the commercially available preperation mixed with magnesium stearate is so insoluble that extraction and parenteral administration is exceedingly improbable. Thus, it seemed that the key question to be answered was whether oral loperamide produced opioid-like subjective effects (or any subjective effects) in supratherapeutic dosage.

Our objective, therefore, was to compare the subjective effects of loperamide with those following a placebo and a threshold dose of an appropriate criterion drug (codeine) in a manner analogous to the study of diphenoxylate carried out by Fraser and colleagues (Fraser et al. 1961) at Lexington in post-addicts.

Study I

Procedures

The first task was to determine an appropriate dose of loperamide to use in a study of abuse potential. Nine paid volunteers were recruited. They were not opiate addicts but had prior experience with other drugs, such as alcohol and marijuana. Subjects participated three at a time in a "dose run-up" on Mondays, Tuesdays and Wednesdays for six weks. They remained in the hospital for 25 hours at each drug trial but were on leave from the hospital between trials. Since preliminary informtion on phamacokinetics of loperamide indicated a $t_{\frac{1}{2}\beta}$ of 12 hours, we were obliged to wait at least 60 hours between tests on the same person. Mindful of this obligation and in order to minimize the effects of varying day of the week, each subject was tested whenever possible on the same day of the week thoughout the study.

Based on data provided by Janssen Pharmaceuticals, we began with a dose of 12 mg loperamide (6 times the usual therapeutic dose). Our research committee gave us permission to raise the dose by 6 mg

increments; however, we were obliged to report on the effects after each 12 mg increment and to obtain specific permission to raise the dose to susbsequnt higher levels. During the weeks when loperamide at 12 mg, 18 mg and 24 mg was being tested against placebo and codeine, each subject's morning dose consisted of 12 capsules containing active drug and/or enough placebo to equal 12 capsules. Loperamide at 30 mg and 36 mg required the subject to ingest 18 capsules; loperanide 42 mg 48 mg, 24 capsules; and loperamide 52 mg and 60 mg, 30 capsules. Sometime during the study all subjects received placebo. Eight of the nine subjects had a test dose of codeine sulfate (96 mg base) which was about 7 percent less than the 103 mg codeine base used at Lexington.

To assess the extent and nature of subjective effects of the substances ingested, we used standard instruments developed at Lexington--the Addiction Research Center Inventory (ARCI)subscales, Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) and Morphine-Benzedrine Group (MBG)--as well as questionnaires asking "Do you feel the drug; do you like the drug; can you identify the drug?" In addition, we measured pupillary responses

Results

Table 1 summarizes the data for the doses used, grouped into three categories: low dose (12, 18, and 24 mg); medium (30, 36, and 42 mg); and high (48, 54, and 60 mg). Despite the absence of systemtic

TABLE 1

SUBJECTIVE POSITIVE RESPONSES TO TREATMENTS--LOPERAMIDE AT THREE DOSAGE LEVELS, CODEINE AND PLACEBO--STUDY I

Treatments	N	Felt Drug		Liked Drug		Ident. as "Dope"	
		2 Hrs	4 Hrs	2 Hrs	4 Hrs	2 Hrs	4 Hrs
Lopermide							
Low(12,18, 24 mg)	9	6 67%	2 22%	4 44%	2 22%	0 0%	1 11%
Medium(30, 36,42mg)	8	4 50%	4 50%	3 38%	3 38%	2 25%	2 25%
High(48, 54,60mg)	9	3 33%	6 67%	0 0%	0 0%	0 0%	1 11%
Codeine	8	6 75%	3 38%	4 50%	3 38%	2 25%	0 0%
Placebo	9	2 22%	2 22%	1 11%	0 0%	0 0%	1 11%

assignment of subjects, we felt comfortable in making the general inference that (1) our subjects were not predominatly placebo reactors and (2) they did not express any particular liking for placebo materials. Our subjects did "feel" our test dose of codeine

and they did "feel" loperamide at doses in the moderate to high levels but did not particularly like the effects.

On the basis of these findings we decided that 60 mg or 30 capsules was as highadose as seemed reasonable to administer to subjects with an established opiate abuse history and to compare with what we thought to be a threshold dose of codeine.

STUDY II

Procedures

Study II involved a double-blind cross-over design using nine subjects who had been active opiate users and who had been withdrawn from opiates for varying periods of time. Some had not been dependent for several years, having stopped using opiates long before the study; others had been withdrawn only within the preceeding two weeks in our research unit. In contrast to Study I, which permitted subjects to be on leave between episodes of testing, Study II was entirely an inpatient investigation and subjects remained as inpatients from at least a day or two prior to their participation in the study until the day after all three test doses had been given.

Based on pharmacokinetic data from Study I which indicated a $t_{\frac{1}{2}\beta}$ of 9 hours (Weintraub et al. 1977) we reduced the minimun interval between test sessions to 72 hours. The three treatments--loperamide 60 mg, codeine sulfate 120 mg (96 mg base), and placebo--were given in random order.

Results

In response to the question, "Do you feel the medication?" at the peak effect for codeine (which occurs at two hours) five of nine subjects (56%) said they felt the medicine whereas only four of nine (44%) of the subjects said they felt loperamide. Only one subject indicated that he felt placebo.

Answers to the question, "Do you like the medication?" were weighted according to a scoring system based on the Lexington formula which assigned increasing scores to various degrees of liking (Fraser et al. 1961). If a subject didn't like the drug at all, the response was scored 0; liking slightly, scored 1; liking moderately scored 2; liking a lot, scored 3. The total score for the group of nine subjects was 6 at peak (two hours) for the dose of codeine and 3 at peak (four hours) for loperamide. For placebo, the highest total weighted liking score for the nine subjects was only 1.

On the ARCI PCAG subscale (generally measuring sedation), this group of subjects showed very little change with placebo, modest increase with loperamide, and a small decrease with the standard dose of codeine. The "change" scores for each subject for two, four and six hours were summed (Jasinski et al. 1975) and the sums were analyzed by a one-way analysis of variance followed by orthogonal contrasts in which loperamide and placebo were contrasted

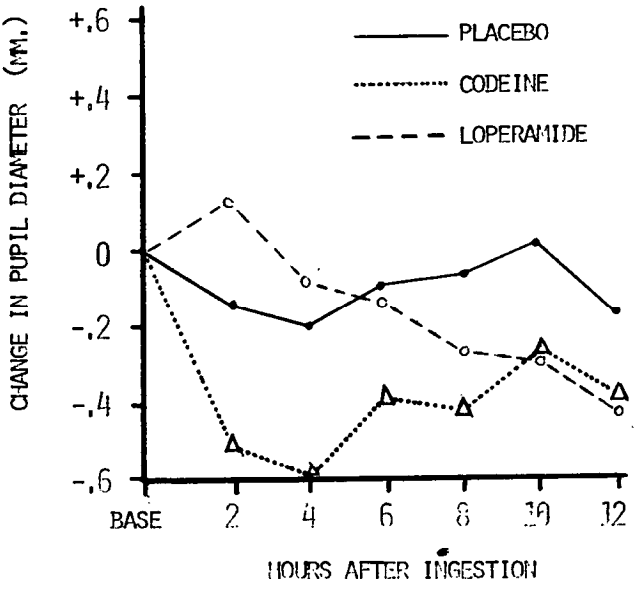
against codeine. On the PCAG subscale, the changes were not statistically significant.

Similar analyses of the responses on the MGB subscale of the ARCI (generally measuring euphoria or stimulation) showed little change with placebo, a consistent elevation with codeine, and, at the two-hour point, a decrease with loperamide. While there was virtually no differerce between loperamide and placebo on this scale, codeine differed from both at the .07 level.

Figure 1 shows the pupillary responses for the three standard drugs. Again, there was virtually no net change in this group with placebo. Codeine showed a statistically significant pupillary constriction which, in general, tended to parallel the psychological effects in terms of time. Here, again, the effects of codeine are distinct from those of loperamide and placebo (.04 level).

In summary, in terms of responses on the scales validated at Lexington and in terms of pupillary responsed, lopermide at 60 mg was distinct from codeine and hardly distinct from placebo. Despite

FIGURE 1



Pupillary responses to placebo, codeine (120 mg) and loperamide (60 mg)--Change from baseline.

this, the subjects taking loperamide did feel some drug effect.

Table 2 summarizes the findings from this study and compares them

TABLE 2

LOPERAMIDE STUDY II VS LEXINGTON SUBJECTS--COMPARISON OF RESPONSES PERTINENT TO ABUSE POTENTIAL

	Lexington	Psychiatric Institute		
	103mg Codeine Base	96mg Codeine Base	60 mg Loperamide	Placebo
Felt drug (at peak)	75%	56%	44%	11%
Identified as dope	33%	44%	11-33%*	11% (4 hours)
Mean weighted liking score (at peak)	1.2 (2 hours)	0.67 (2 hours)	0.33 (4 hours)	0.11 (4 hours)

*Only one subject called the drug "dope" without qualification. Two additional subjects refused to choose between dope and another category, likening the effect to tranquilizer/goofballs/hallucinogen/dope combinations

with findings obtained in post-addicts at Lexington. It shows three parameters: the percentage of subjects who indicated they "felt" a drug effect: the percentage of subjects who identified the drug effect as being like "dope"; and the man weighted "liking" score for the group of subjects studied. The weighted liking score was based on the procedure developed at Lexington (described above); the scores for all subjects were summed and divided by the number of subjects toproduce the mean.

When 140 mg of codeine phosphate (equal to 103 mg of codeine base) was tested at Lexington, it was felt by 75 percent of ex-addict subjects but it was identified as "dope" by only 33 percent of such subjects, indicating, again, that in such subjects who have, on average, been off opiates for a minimum of a few months, 103 mg of codeine base is a threshold dose in terms of subjective effects. The mean weighted liking score for these subjects at Lexington was 1.2, indicating that for most subjects their liking for such dosage was, at best, slight.

Table 2 also shows the results from the three drugs given in our cross-over study with more recently detoxified addicts. Only one subject (11 percent) felt a drug on placebo, identified placebo as "dope" and liked it slightly. Our dose of codeine, which was only 96 mg of codeine base, was felt by 56 percent of our subjects and identified as "dope" by 44 percent. These percentages suggest that our subjects may have keen slightly less sensitive (or more tolerant) but also more discriminating. The mean weighted liking score for our nine subjects was 0.67 or approximately half that reported by Lexington. Since only 56 percent even felt this dose of codeine as a drug, it is not surprising that the average liking score was lower than that at Lexington.

After 60 mg of loperamide, 44 percent of the nine subjects indicated they felt sane drug effect at peak. At that time (approximately four hours) 11-33 percent of the subjects identified the drug effect as being like "dope". In the case of codeine there was little hesitation in describing the effect as like "dope", but only one subject made such an unequivocal identification after taking loperamide; two others refused to make a clear cut discrimination, indicating that it might be a mixture of dope and tranquilizer, and, in one case, dope and marijuana. If we count all cases where the word "dope" was mentioned to any extent, no matter how qualified, we come up with 33 percent. If we insist that the identification be as unequivocal as that observed with codeine, then the figure drops to 11 percent--the same figure obtained with placebo.

The weighted liking score for loperamide was 0.33, about half of that obtained with our threshold dose of codeine, which, in turn, was only about half that obtained by a slightly larger dose of codeine in addicts who had been detoxified for a longer period at Lexington.

In summary, our study indicated that 60 mg of loperamide at 15 to 30 times the recommended therapeutic dose in the marketable dosage form produced a detectable subjective effect in a little less than half a group of subjects with a known opiate abuse potential, was liked little or not at all, and was identified as "dope" at a frequency less than that for a threshold dose of oral codeine.

We believed on the basis of these findings that given the social context in which the drug is likely to be used and sold, the abuse potential of loperamide was probably low enough so as to make any formal controls unnecessary. Given this indication of an exceedingly low abuse potential, it seemed reasonable to allow the market place to provide further indication as to whether or not the low level subjective effects produced with supratherapeutic doses of loperamide would be abused. We conceded, however, that the results were not 100 percent negative. Supratherapeutic doses were not found to be aversive by all subjects. But we predicted that there would be little or no abuse of this substance as long as drugs like codeine in cough medicine, paregoric and diphenoxvlate were available at much lower costs. At that time (1976) this recommendation was not accepted by F.D.A. Loperamide was placed in Schedule V of the C.S.A.

PROBLEMS IN THE USE OF NONPRISONER SUBJECTS

We encountered several distinct problems in doing the dose run-up Study I in normal volunteer subjects--the institutional requirements, the anxiety of the subjects and the staff, and the real-life circumstances from which the subjects came and to which they returned between drug trials. Because the drug dosage was raised step wise to a level which far exceeded the therapeutic dose, the institution's Review Board required that the subjects be hospitalized--overnight at least. In addition to the large amount of red tape and/or paperwork this requirement entailed, formal admission made the subject a "mental" patient who was "out on pass" between experimental trials.

The everyday life of the subjects between trials differed widely across subjects. Some worked at night and might arrive on an experimental morning in a fatigued state and looking forward to a day of rest. Others might have been affected by pretesting indiscretions in eating and drinking. In order to control the subject's behavior on the night before an experimental trial, the subjects were offered an extra fee if they would come into the hospital the evening before. Some took advantage of the option but, within the limits of incentives permitted, this approach was not entirely successful.

Problems were not encountered where they had been anticipated--in keeping subjects occupied. They had access to a color TV, to ping pong, to an outdoor basketball court, and to a staff-accompanied walk in the evening. Apparently the experimental day did not tax their patience unduly. Such would not have been the case if we had required complete hospitalization for the duration of the study--as in Study II, where holding the subject in the hospital for the duration of the study was very difficult. Therefore, despite the variability introduced by the differences in subjects' real life happenings, the experimental procedure of requiring only twenty-five hours hospitalization for each trial was probably a satisfactory compromise with the realities of costs, subject recruitment and adequate control of experimental variables.

Study II, which required the use of detoxified ex-addicts, posed more perplexing problems. Was it ethical to administer a drug that might have opioid-like effects to a former user? How could we be sure that the subject was fully detoxified? However, the major problems we encountered as the study unfolded were in recruiting suitable subjects and then dealing with their perception that once we had "invested" in treating their withdrawal, they were under no obligation to participate in the research. This perception was, of course, not without basis. As part of our informed consent, we were obliged to assure potential subjects that a decision not to participate would not affect their treatment. In some cases, subjects would complete detoxification, participate in part of the study and then, recognizing our commitment to data acquisition and our investment in them as individuals, they would seek to renegotiate the fee for participation.

Despite these problems the study was completed, and the central question of whether selected studies of abuse potential can be conducted in nonprisoner volunteers can be answered in the affirmative. The issue of whether it would be possible to test the capacity of an unmarketed drug to induce physical dependence in supratherapeutic dosage is unresolved.

EPILOGUE

Recently, at an F.D.A. hearing, Ortho Corporation, which markets loperamide (as Imodium), presented data indicating that after 2 1/2 years of marketing with an estimated 80 million doses prescribed to more than 3 million patients there have have been no reported overdose deaths and only one DAWN system equivocal report of use by a drug abuser. On the basis of these data and the fact that the drug is

available but uncontrolled in 70 other countries, the F.D.A.'s Advisory Committee has recommended complete decontrol. It is not unfair to point out that in this situation, as in others, the data from human testing proved to be a better predictor of abuse potential. than various animal models.

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Acute Tolerance to Cocaine in Humans

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ABSTRACT

It has been shown that there is a dose-response relationship between blood levels of intravenously injected cocaine and magnitude of evoked heart rate (Javaid et al. 1978). This relationship also holds for inhaled cocaine while plasma levels are increasing, but the cardiovascular effects of the drug dissipate more rapidly than cocaine disappears from the plasma. This suggests that the repeated administration or sustained blood level of cocaine might produce an acute tolerance. Using an intranasal route of administration it is possible to maintain cocaine blood levels for a substantial period of time after heart rate begins to decrease from its peak levels. If an intravenous dose is then administered on top of this preexisting blood level, the effects of this second dose can be compared to the same dose administered to subjects with no preexisting blood level.

Eight normal adult volunteer subjects were tested according to this design with intravenous saline and cocaine ranging in dose from 16 to 48 mg. Each intravenous injection was administered one hour after inhalation of placebo, when no cocaine plasma levels were present, or 96 mg, when cocaine plasma levels were elevated. Cardiovascular effects and verbal report of drug effects were monitored for eight hours daily. The data suggest an acute tolerance to the initial effects of cocaine during the first hour after intravenous drug. When cocaine was intravenously administered to subjects who previously inhaled 96 mg during the same experimental session, there was a smaller change in heart rate, subjective rating, stimulant scale scores on the Addiction Research Center Inventory, and Arousal and Positive Mood factor scores on the Profile of Mood Scales than when the intravenous dose was the only cocaine those subjects received during that experimental session. No long-term cocaine tolerance was noted.

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ACKNOWLEDGMENTS

This research was supported by DA-01491 and DA-00024 from the National Institute on Drug Abuse and RR-00055 from the National Institutes of Health.

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A Study of Hospitalized Surgical Patients on Methadone Maintenance

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INTRODUCTION

The study described below addresses itself to the problem of Methadone Clinic clients who require hospitalization for routine surgical procedures or for traumatic episodes. Such individuals would have pain, and, under such circumstances, should be legitimately treated by conventional narcotic medication added to their maintenance methadone. They may also manipulate the episode to inappropriately receive incremental doses of narcotics, since pain is a subjective symptom (Rubenstein et al. 1976).

In either of these two circumstances, it was hypothesized that due to previously induced tolerance to narcotics, a further increment in methadone dosage might ensue and that? in the long run, more far-reaching effects on eventual detoxification and methadone dosage reduction might conceivably occur.

In order to study this possibility, 25 patients from the Methadone Clinic at Bellevue Hospital in New York City, who had been hospitalized for surgical procedures and traumatic episodes, were compared with 25 methadone clients from the same hospital facility matched as to age, sex and length of time in a methadone program. Since this was a retrospective study, it is recognized that the control group, by the very fact that they were there to be chosen, are not strictly a control group with respect to detoxification and rehabilitation from the program. Hospitalization and treatment of pain with added doses of narcotics may jeopardize the chance for subjects to have decremental doses of methadone, eventual detoxification and possible rehabilitation from drug abuse (Dole at al. 1966).

STUDY POPULATION

Written informed consent was obtained from all 50 study subjects. As can be seen from Tables I and II, the mean dates for entry into the methadone program were similar between the hospitalized group and the control group. Similarly, the mean age and the mean dose of initial methadone were essentially similar between the two groups.

TABLE I. NON-HOSPITALIZED PATIENTS

CLIENT NO.	SEX	STUDY ENTRY TO PRESENT (MONTHS)	AGE AT END OF STUDY	METHADONE (MGM.) DAILY DOSE AT TIME OF ENTRY	METHADONE (MGM.) DAILY DOSE AT END OF FOLLOW-UP	NOTE
1	M	74	31	90	70	
2	M	69	46	100	100	
3	F	5	21	20	40	
4	M	42	28	80	80	
5	F	12	30	30	30	
6	F	53	25	80	80	
7	M	14	43	60	70	
8	F	69	24	60	80	
9	F	18	25	20	60	
10	M	9	45	100	100	
11	M	16	34	100	70	
12	F	74	35	80	80	
13	M	24	27	60	60	
14	M	60	31	60	70	
15	F	61	28	80	80	
16	F	37	28	40	5	Left treatment
17	F	75	25	90	60	
18	M	18	28	60	35	Transferred
19	F	38	25	80	30	
20	F	14	35	70	60	
21	M	25	30	50	50	
22	M	4	27	20	30	
23	F	27	25	100	60	
24	F	31	24	40	20	Left treatment
25	M	77	32	80	70	
MEAN RANGE		27 4-77	28 22-46	60 20-100	60 5-100	

With respect to the hospitalized group, the mean length of hospitalization was 9 days and the mean follow period after hospitalization to the date of the end of the survey was 20 months. In addition, the prehospitalization methadone dose of each individual is noted in a separate column and, following that, the post-hospitalization dosage.

Table III depicts the causes for hospitalization of the hospitalized group. Following that is a summary in the same Table of the doses of analgesic received by each of these individuals. The numerical designation of the subjects in this particular Table is the same as that of Table II and forms the basis for further data analysis below.

RESULTS

It will be noted that there is little essential difference between the methadone dosage for the hospitalized group and for the non-hospitalized group after a similar period of followup time and that the range of dosage is similar between the two groups. In addition, it is obvious that the hospitalized group were discharged and immediately followed in their respective methadone clinics on doses

TABLE II. HOSPITALIZED PAIETN

PATIENT NO.	SEX	SLTUDY ENTRY TO PRESENT (MONTHS	AGE AT STUDY STUDY	METHADONE (MGM.) DAILY DOSE ON ADM. TO HOSP.	METHADONE (MGM.) DAILY DOSE ON DISCH. FROM HOSP.	NO. OF DAYS IN HOSPITAL	METHADONE (MGM.) DAILY DOSE AT END OF STUDY
1	F	36	33	70	70	27	50
2	M	60	29	60	60	43	40
3	F	12	29	50	50	10	40
4	M	24	24	70	70	10	70
5	F	24	23	70	70	2	60
6	F	24	25	40	40	12	40
7	F	48	25	60	40	2	50
8	F	6	25	60	60	12	50
9	M	36	37	90	90	29	90
10	F	72	30	60	60	6	5
11	F	72	38	90	90	2	5
12	M	24	39	40	40	7	5
13	F	24	23	40	10	14	15*
14	M	12	27	60	60	5	20
15	F	12	21	50	50	8	40
16	M	48	44	80	80	10	◘
17	F	24	23	50	50	7	10
18	M	36	32	80	80	5	100
19	M	72	29	90	90	21	60
20	M	36	32	90	90	18	90
21	M	36	34	80	80	9	50
22	F	24	28	50	50	5	15*
23	M	365	46	80	80	3	80
24	F	60	25	90	70	9	70
25	M	24	36	80	70	3	50
MEAN		39	29	70	70	9	50
RANGE		6-72	21-46	30-90	40-90	2-43	5-100

△ Terminated * Discharged ◘ Died

essentially the same as those on which they entered the hospital. It is also apparent that irrespective of the entering dosage of methadone for the hospitalized subjects or the amount of narcotic analgesics required during their hospitalization, the outcome did not affect their discharge dosage and subsequent methadone dosage.

DISCUSSION

Several of the hospitalized patients were transferred to other methadone clinics and their subsequent course determined by inquiry. In addition, a number of this group became detoxified and discharged from the clinic or discharged for administrative reasons. Because of the nature of the selective process, these resolutions were not available to the control group and, therefore, conclusions based on that particular difference are not valid in this study. Changing conceptions of methadone maintenance dosage may also confound comparison between the two groups, since the study subject population extends from 1972 through 1978. For the same reason, abuse fashions may have changed in such a way as to further confound such comparison. On the other hand, the matching of subjects by age, sex, and length of residence with the program allows some conceptual comparisons between the two groups.

TABLE IIIa. HOSPITALIZED PATIENTS

DIAGNOSIS	NARCOTIC AND ANALGESIC DRUGS IN HOSPITAL
1. Low back pain, post intramedullary fixation of left femur	DI 50 mgm. X 74 P 65 mgm. X 16 MO 70 mgm. X 27
2. Ureterits cystical, hydronephrosis, cystoscopy, bladder biopsy	MO 50 mg. X 16 MI 30 mgm X 6 DI 75 mgm. X 75 MO 40 mgm. X 15 MI 20 mgm. X 1 DI 100 mgm. X 20 MO 30 mgm. X 2 MI 10 mgm. X 20 DI 50 mgm. X 13 CO 60 mgm. X 8
3. Post vabra pelvic inflammatory disease and non-specific inflammation of recto-sigmoid of on-known origin	MO 50 mgm. X 9
4. Pancreatitis, appendicitis	MO 70 mgm. X 9 AN 650 mgm. X 1
5. Voluntary interruption of pregnancy	MI 20 mgm. X 1 MO 70 mgm. X 1 P 65 mgm. X 4
6. Ruptures spleen, raped, pregnant, splenectomy. culdocentisis	DI 75 mgm. X 1 MS 4 mgm. X 1 DI 75 mgm. & phenergan X 15
7. R/O ectopic pregnancy, laparoscopy, DSC	MI 10 mgm. X 1 MO 60 mgm. X 1
8. Bilateral salpingitis, appendectomy	DI 75 mgm. X 5 MI 15 mgm. X 6 AN 650 mgm. X 1 MO 60 mgm. X 10 MI 30 mgm. X 2 P 65 mgm. X 11
9. Chronic active hepatitus, hyperspleenism, thrombocytopenia, right mastoidectomy	DI 100 mgm. X 1 AN 650 mgm. X 2 MO 90 mgm. X 28 P 65 mgm. X 17
10. Chronic lymphatic observation of left arm, cellutis of left hand	MO 60 mgm. X 4 ASA 650 mgm. X 3 PN 50 mgm. X 3
11. Intrauerine pregnancy, abortion by suction and curettage	MI 30 mgm. X 1 MO 90 mgm. X 1 MO 30 mgm. X 1
12. Chronic relal failure, AV fistula of left arm	MO 40 mgm. X 3 AC 2 tablets X 3 MO 15 mgm. X 2 CO 30 mgm. X MI 15 mgm. X 1
13. Liver abscess. Fitzhugh-Curtis syndrome	MI 10 mgm. X 1 MI 30 mgm. X 13
14. Right hernia repair	MO 60 mgm. X 4 MI 60 mgm. X 1 DI 75 mgm. X 2
15. Repeat cesarean section	MO 50 mgm. X 7 CO 60 mgm. X 4 MI 10 mgm. X 2 DI 75 mgm. X 6
16. Cellulitis abscess dorsum left foot, debridement	DI 75 mgm. X 2 MO 80 mgm. X 7 MO 50 mgm. X 2
17. Voluntary interruption of pregnancy	MO 50 mgm. X 3 MI 25 mgm. X 1 CO 60 mgm. X ?
18. Fractured rib, pneumothorax	MO 80 mgm. X 8 AN 650 mgm. X 1

TABLE IIIb. HOSPITALIZED PATIENTS

DIAGNOSIS	NARCOTIC AND ANALGESIC DRUGS ADMINISTERED IN HOSPITAL
19. Right hydronephrosis secondary to uretero-pelvic junction obstruction, status post right nephrectomy	MO 90 mgm. X 19 MO 30 mgm. X 18 MI 40 mgm. X 2 DI 75 mgm. X 3 MI 30 mgm. X 4 DI 50 mgm. X 1
20. Cominuted fracture of fight tibia	MS 10 mgm. X 4 MO 60 mgm. X 3 MO 10 mgm. X 8 MO 70 mgm . X 2 MO 5 mgm. X 7 MO 80 mgm. X 3 MO 90 mgm. X 4
21. Right inglnal hernia repair	DI 30 mgm X 11 MO 80 mgm. x 7 AN 650 mgm. X 7
22. Mia forcepts delivery, median laceration and repair	MO 50 mgm. X 5 P 65 mgm. X 4 CO 60 mgm. X 1
23 Chronic oltitis median of left ear, left maltoectomy	MO 80 mgm. X 3 MI 40 mgm. X 1 MO 40 mgm. X 1
24. Cesarean section	DI 50 mgm. X 8 P 15 mgm. X 1 DI 75 mgm. X 1 MD 90 mgm. X DI 100 mgm . X 1
25. Fracture left mandible, closed reuciton	MO 80 mgm. X 1 MO 70 mgm. X 1 DI 50 mgm . X 3

MIDICATION CODE

ASA = Aspirin PO
CO = Codeine PO
DI = Meperidine IM
MI = Methadone im
MO = Methadone PO
AC = Aspline 325 mgm. & Codeine 30 mgm. (combination)
MS = Morphine Sulfate IM
P = Propoxyphene PO
AN = Acetaminophen PO
PN = Pentazocine PO

In this retrospective study, the house staff, with their attendings on a teaching service, had little or no guidance as to the management of pain under these circumstances. Therefore, there is a wide spectrum of treatment philosophies represented in terms of analgetic management. Patients number 1 and 2, for example, were treated with large amounts of narcotics added to their maintenance methadone over prolonged hospitalization. On the other hand, patients number 9 and 19 were also hospitalized over prolonged periods and received relatively little extra analgetic medication. In four instances, in short term hospitalization (patients 5, 7, 10, 24), patients in house on oral maintenance methadone had their doses lowered slightly to "balance" added narcotics. Sometimes this was completely inappropriate, as in patient number 10 who received added aspirin and pentazocine. Two patients (4, 18) were treated with analgetics other than narcotics, and one patient (3) received no added analgetics at all although he expressed a considerable complaint of pain.

Analysis of the data reveals that the mean methadone dosage for the study patients was 70 mgm. This would be traditionally considered "high dosage" maintenance. Despite this, these patients required only standard dosages of narcotic analgesics to control pain. Thus, any concept that supernormal dosages need be utilized acutely to overcome "methadone blockade" is not supported. Only 3 patients in the study group would be considered to be receiving "low dosage" maintenance (i.e., below 50 mgm/day). However, even here repeated doses by various routes of narcotic analgesics did not appear to increase methadone dosage requirements on discharge.

In our study, when a maintenance dosage of methadone was to be given parenterally, the total dose was reduced by one-third to

one-half with half the reduced dosage given at 12-hour intervals. We feel this method more closely approximates a patient's oral maintenance dosage and, as such, is unlikely to provide analgesia in addition to the other drugs employed. We have used this method of parentemal maintenance dose reduction extensively at Bellevue Hospital with no clinical problems of oversedation or methadone withdrawal symptoms being manifested.

In this study, drug interaction could obsure a patient's need for an enhanced methadone dosage, Reviews of in-hospital medication records revealed no medical use of interacting drugs during hospitalization in our patients. On hospital discharge, urine profiles did not reveal any consistent abuse of sedatives or antidepressants by the study patients. Indeed, urine profiles for the month preceding hospitalization and the month after discharge show no significant change in substance abuse patterns for the group (Table IV) (N.U.C. Methadone Maintenance Treatment Program, 1979 Census Date, Bi-Weekly Report).

TABLE IV. URINE TESTS

	STUDY GROUP		CONTROL GROUP
	Pre-Hospital (1 mo.)	Post Hospital (1 mo.)	
Total No. Urines Analyzed	46	74	50
No. "Dirty"	9	17	12
% "Dirty"	19.6	22.9	24.0
Drugs Abused	H A B C V P NM	H A B C V P NM	H A B C V P NM
No. of Mentions	0 1 1 1 2 0 4	5* 0 1 3 1 1 6	3 2 2 2 1 0 2
% Total Urines	0 2.2 2.2 2.2 4.4 0 8.7	6.8 0 1.4 4.0 1.4 1.4 2.1	6.0 4.0 4.0 4.0 2.0 0 4.0

* Accounted for by one patient

TOTAL N.Y.C. MMTP BI MONTHLY URINE TESTS

	1976	1977	1978
% "Dirty"	24.0	26.0	30.0
% Drugs of Abuse	H = 7.0 B = 4.0 A = 2.0 C = 9.0 D = 14.0	H = 9.0 B = 4.0 A = 1.0 C = 9.0 O = 6.0	H = 9.0 B = 4.0 A = 7.0 C = 6.0 O = 9.0

Because study patients were hospitalized in several different years, this Table is provided to give a representative sample of substance pattern

CODES

A = Amphetamine
B = Barbiturates
C = Cocaine
H = Heroin
O = Other (placidyn, alcohol, elavil, etc.)
P = Phenothiazine
V = Valium
NM = Neg. Methadone

TABLE V. CLIENT OUTCOMES

	Hospitalized N (%)	Control N (%)
Stable Maintenance at Bellevue MMTP	15 (60)	15 (60)
Successfully Detoxified from Methadone	5 (20)	5 (20)
Transferred to Another MMTP	4 (16)	5 (20)
Deceased	1 (4)	0 (0)

Thus, although the clinical response may vary, it seems prudent at this time to utilize, when necessary, standard dosages of narcotic drugs in methadone-maintained patients, increasing these dosages only after careful clinical evaluation. It appears that these agents may be used safely and effectively in this patient population without fear of compromising further rehabilitation progress (Table V).

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ACKNOWLEDGEMENT

Supported by the National Institute on Drug Abuse, Grant #DA01679.

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Plasma Levels of Δ^9-Tetrahydrocannabinol After Intravenous, Oral, and Smoke Administration

A. Ohlsson, J.-E. Lindgren, A. Wahlen, S. Agurell, L. E. Hollister and H. K. Gillespie

In the Western countries Δ^9-tetrahydrocannabinol (THC) - the major psychoactive compound in Cannabis - is generally administered by smoking marijuana (0.5-2 percent THC) or hashish (4-10 percent THC), but in Asia the oral intake of various Cannabis preparations is usually preferred. The subjective effects of THC in man after these routes of administration as well as after infusion are well documented (Agurell et al. 1976, Domino et al. 1974, Hollister and Gillespie 1973, Hosko et al. 1973, Lemberger et al. 1972, Lemberger and Rubin 1976 and Perez-Reyes et al. 1973a, 1973b).

The low doses of THC needed for behavioral effects and the rapid distribution and metabolism of THC make it difficult to measure the nonlabelled compound in biological fluids. However, during the last decade various methods (e.g. mass spectrometry, radioimmunoassay or other techniques) have been developed for this purpose (Vinson 1979, Willette 1976). Still, the available information on plasma level of THC is scanty and seldom related to clinical effects.

The purpose of the present investigation was to estimate the systemic availability - as evident from the plasma concentration profiles - after smoking and oral intake of THC in comparison with intravenous administration of the drug and also to evaluate drug effects in relation to the plasma levels of THC after all three routes of administration.

METHODS

Subject and dosage procedure. Eleven men between 18 to 35 years with previous experience with the drug volunteered to participate. The following three forms of THC were administered to each subject in randomized order:

Smoking - Cigarettes were prepared from marijuana material containing 1.64 percent THC and 0.23 percent cannabinol. Each cigarette contained 14.9 to 16.1 mg THC.

Intravenous administration - Five mg of THC in 95 percent ethanolic solution (2 mg/ml) was slowly injected over a period of 2 minutes.

Oral administration - Each subject ate one chocolate cookie containing 20 mg THC.

Blood specimens were drawn at periods indicated in figure 1. The subjects, dosage and sampling procedures have been described in detail elsewhere (Ohlsson et al. 1980).

Analysis of THC in plasma. The plasma levels of THC were determined by a mass fragmentographic method based on the use of deuterated internal standard as previously described (Agurell et al. 1979, Ohlsson et al, in Willette 1976, Ohlsson et al. 1980). The detection limit has been estimated to be 60 pg/ml plasma.

The areas under the plasma concentration versus time curves (AUC) for the time period 0 - 360 minutes were estimated using the trapezoidal role as described earlier (Ohlsson et al. 1980).

Clinical evaluation of drug effects. The following clinical evaluations were made:

a) Pulse rate was read constantly through an ear lobe monitor.

b) Conjunctival injection was rated on a 0 to 4 scale at the same time periods as the blood samples were drawn.

c) A rating of the degree of high on a 0 to 10 scale was made by subjects at periods indicated in figure 2.

RESULTS AND DISCUSSION

Injection. The mean (± SD) plasma concentration versus time curves after injection, smoking and oral administration of THC for the eleven subjects are shown in figure 1. Three minutes after cessation of the 2-minute infusion of 5 mg THC, high plasma levels ranging from 161 to 316 (mean 219) ng/ml were reached. The THC levels in plasma fell rapidly to a few ng/ml during the first hour after administration. The plasma levels decreased rather uniformly with time with little interindividual variation (cf. figure 1). Previously, THC levels have been measured after infusion of 5 mg THC over 30 minutes resulting in initially lower plasma levels (Wall et al. in Willette 1976). After one hour the levels following the 30-minute infusion were similar to those after 2-minute infusion as shown herein.

Smoking. Smoking the marijuana cigarettes resulted in a delivery of 11.6 to 15.6 (mean 13.0) mg of THC which produced peak plasma levels in the range of 33 to 118 (mean 77) ng/ml plasma. As evident from figure 1, a fast absorption was followed by a biphasic plasma decay curve during the first four hours. The similarities to the intravenous curve are striking. The plasma levels determined by us agree well with reported data for ^{14}C-labelled (Lemberger et al. 1972), nonlabelled THC (Valentine et al. in Vinson 1979, and Williams et al. 1978) and also the Δ^8-THC isomer (Agurell et al. 1976).

Oral administration. Despite the higher dose (20 mg THC) by this route, maximum plasma level of THC was between 4.4 and 11 ng/ml (figure 1). In most subjects the peak plasma level was reached at 60 or 90 minutes but in two subjects as late as 240 and 300 minutes. Also, in most subjects more than one plasma level peak could be observed. However, a rapid absorption in a subject did not necessarily confer a high oral systemic availability. Compared to infused and inhaled THC the oral THC yielded low and irregular plasma concentrations.

System availability. The mean AUC for the time 0 - 360 minutes for the three routes of administration and the systemic availability for THC after smoking and oral administration are given in table 1. The systemic availability for THC has been estimated assuming linear pharmacokinetics, i.e. the fraction absorbed is independent of the dose.

TABLE 1

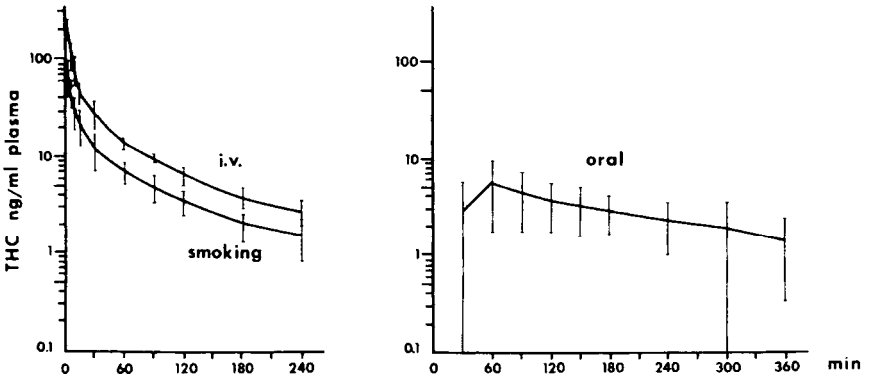
Pharmacokinetic parameters for describing Δ^9-THC disposition following intravenous, smoke and oral administration in eleven healthy volunteers.

Administration		$AUC_{0-360\ minutes}$ [a]	Systemic Availability %
Route	Dose	Mean ± SD (range)	Mean ± SD (range)
Infusion	5.0 mg	4.33 ± 0.62 (3.39 - 5.67)	
Smoking	13.0 mg[b]	1.96 ± 0.65 (0.87 - 2.73)	18 ± 6 (8 - 24)
Oral	20.0 mg	1.02 ± 0.32 (0.72 - 1.60)	6 ± 3 (4 - 12)

[a] pg . ml^{-1} . min.

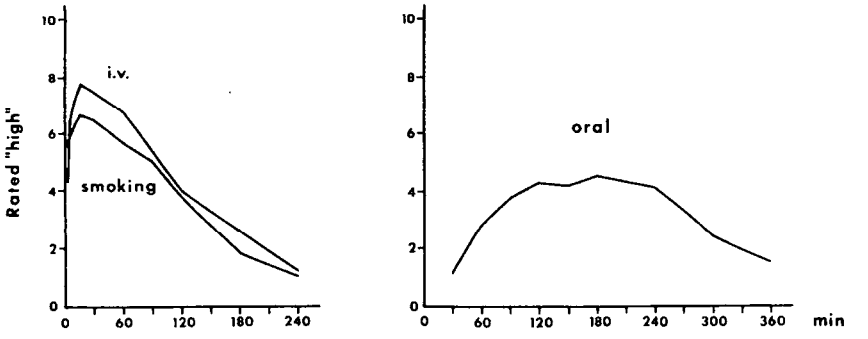
[b] Estimated after subtraction of the remaining THC in the butt (Agurell and Leander 1971). The mean value is presented.

FIGURE 1



Average (± SD) plasma levels of Δ^9-THC in eleven healthy volunteers administered Δ^9-THC intravenously (5 mg), orally (20 mg) and by smoking (mean 13 mg).

FIGURE 2



Time-course of the subjective "high" after all three routes of administration.

An early assumption that THC is about three times as potent when smoked as when taken orally (Hollister and Gillespie 1973) is confirmed by our results. The systemic availability of THC was estimated to 18 ± 6 (SD) percent following smoking and 6 ± 3 percent after oral ingestion (table 1). The 82 percent loss by the pulmonary route is undoubtedly due mainly to pyrolysis and the side stream smoke. The low systemic availability of oral THC may not only depend on a high first pass effect but also to chemical break-down in the gastric juice or to microbial transformation in the gut flora.

Clinical effects in relation to plasma concentrations. Reddened conjunctivae, one of the two most reliable signs of Cannabis intoxication, persisted for as long as levels of THC were above 5 ng/ml. Tachycardia, the other clinical sign, was a less reliable measurement of prevailing levels of THC or "high."

The time-course of the average "high" after the three administration routes is shown in figure 2. After both infusion and smoking, a prompt onset and steady decline of the effect occurred over a four-hour period. Following oral ingestion, the onset of the subjective "high" was much slower but lasted longer. Also, the clinical effect occurred at lower plasma concentrations by this route than after infusion and smoking. The appearance of "high" lagged behind the plasma concentrations (cf. figures 1 and 2). The correlation between the degree of intoxication and log concentrations of plasma THC were, therefore, not especially strong.

In summary, the plasma levels may not necessarily reflect the levels within the brain and one might surmise that a slow absorption of the drug permits a larger fraction to penetrate the blood-brain-barrier. Also, after oral intake of THC the formation of the psychoactive THC metabolite 11-hydroxy-THC is probably more abundant than after infusion and smoking.

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ACKNOWLEDGEMENTS

We thank Ms. I. Emanuelson and I. Jansson for skillful technical assistance. This work was supported by the Swedish Medical Research Council, grant DA-00424 and the Research Services of the Veterans Administration.

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Marijuana and Driving

A. J. McBay and S. M. Owens

Alcohol continues to be, and will most likely always be, the principal drug which causes deterioration of driving performance. In North Carolina for over 10 years, the bloods of more than half of the operators (57%) killed in single vehicle crashes contained more than 0.09% alcohol. The effects of drugs other than alcohol on driving are virtually unknown. Only recently have attempts been made to see if other drugs have adverse effects that could lead to accidents. The contribution of other drugs with and without alcohol should be ascertained.

There is concern that the use of marijuana may increase the risk of having an accident. In order to establish this scientifically, it will be necessary to show that operators are being adversely affected by the drug and that they are over-represented in the group of drivers having accidents compared to a non-accident group.

To obtain such information it is necessary to analyze bloods from a random sample of the non-accident driving population and also from operators involved in crashes. It is becoming increasingly difficult to obtain blood from living operators. This is not true of operators killed in crashes. If a drug is rarely found or occurs at a non-influencing concentration in the blood of those killed in crashes, the drug is a relatively insignificant factor in crashes and it is not necessary to establish the incidence of the drug in the general driving population.

Information which may be of questionable value in evaluating the effects of drugs on driving is based on anecdotal or hearsay statements, laboratory tests of physical or mental impairment, laboratory driver simulators , test course performance, and actual street-driver performance. A report published in 1977 reviews the literature up to that time(1). Little has been added since that time. Regardless of the results of the above methods of ascertaining impairment they do not answer the question of whether the use of a certain drug has an adverse effect on driving. This question may best be answered by determining the concentrations of drugs in the bloods of a signifi-

cant number of operators involved in crashes which are not attributable to some other cause. Evidence of crashes which might be attributable to operators adversely affected by marijuana is very rare. Peripheral studies have indicated that marijuana may cause problems but not-for a very significant number of operators.

An early and widely cited report on drivers allegedly under the influence of marijuana, who might have caused fatal accidents, was based on hearsay. This is the report of Sterling-Smith et al. (1976). They concluded that 43 out of 267 (16%) of the drivers were under the influence of marijuana (2). The results were based on interviews of friends and relatives of the deceased. Only 13 (5%) were said to have used only marijuana. The "risk taking behavior" of marijuana smokers was rated as low and in the same category with "driving without restraints" or "smoking more than 2 packages of cigarettes daily." Since there was no evidence that there were any marijuana constituents in the blood of any operators it is doubtful that this report sheds any light on a possible safety problem that might be due to the effects of smoking marijuana.

Teale (1977) reported on the examination of 66 bloods obtained from fatally injured drivers (3). The bloods were analyzed by radioimmunoassay for cross-reacting cannabinoids, which were found in 6 specimens. Three of the blood extracts were purified by high pressure liquid chromatography to separate the tetrahydrocannabinol (THC) from the other cannabinoids. Blood of one of the victims contained 2.3 ug/L of THC and 0.34% of alcohol. The other two victims were motorcyclists who crashed into automobiles. Their bloods contained low concentrations of THC, 1.5 and 4.4 ug/L. Because cannabinoids persist in the blood for many hours, it is not possible to assess the effects these low concentrations of marijuana had on the operators. This is rather a small sample to draw any valid conclusions.

Reeve in 1979 reported on the examination of bloods from 1792 people arrested for driving under the influence (4). Blood was analyzed for THC by a radioimmunoassay. Unfortunately, the procedure used was not adequately enough documented to establish its sensitivity (5 ug/L). Of the 1792 operators, 281 (16%) had positive findings of THC in their blood, 111 of the 281 had blood alcohol concentrations exceeding 0.09%. Most specimens were not analyzed for other drugs. A strong negative correlation was found between the THC positive bloods and accidents. The value of this study as an indication of the safety of driving under the influence of marijuana is questionable.

A Canadian study (1980) sought drugs in 401 fatally injured drivers and THC was found in the bloods of 14 (3.5%) of the victims, but 7 of the 14 had more than 0.09% alcohol in their blood. The bloods of 2 of the drivers contained 5 ug/L of THC; the rest had less than 3 ug/L of THC (5).

The literature does not reveal that marijuana is a factor in unsafe

operation of a motor vehicle. Sparse as the reports may be, they tend to show that if there are drivers who are unsafe because of marijuana, their numbers are small and most are also influenced by alcohol.

METHODS

The 100 cases chosen for this study were those where adequate and suitable specimens of blood were obtained from dead operators who were killed in single vehicle crashes. Specimens from those who lived more than 1 hour or whose blood was unsuitable because of decomposition or contamination by embalming fluid were excluded.

The blood specimens were analyzed by RIA for THC using an Iodine-125 tracer (6). Only 0.1 ml of plasma or blood was required. The sensitivity was at least 0.3 ug/L for plasma and 1.1 ug/L for hemolyzed blood. The antiserum cross reacted with 11-hydroxy THC about 20%, but, fortunately, this physiologically active metabolite is present in blood in low concentrations (7) following marijuana smoking. It may be a significant factor when marijuana is ingested orally. The other major metabolite, 11-carboxy THC, which is physiologically inactive, is present in blood in significant quantities but fortunately cross reacted less than 0.1%. The analysis was further tested by analyzing specimens obtained from controlled smoking studies (Fig. 1). No specimen which contained less than 3 ug/L of THC was reported as positive.

RESULTS AND DISCUSSION

The safety of driving following the smoking of marijuana will have to be established. In our opinion, this has not been done. Smoking studies reveal that the concentration of THC peaks in the blood at about 50 to 150 ug/L, depending on the dose, in minutes while still smoking. The concentration drops to about half that in about 10 minutes, and to less than 10 ug/L in about an hour. The reported high lasts about two hours (8). No reports were found which indicated that during the time the person was "high" their driving performance was affected.

The concentration of THC found in the victims in this study ranged from 3 to 18 ug/L with a median of 5 ug/L. At this time we are unable to assess the effects of such concentrations on driving ability (Table 1).

We do not know the significance of 18 ug/L of THC combined with 0.11% of ethanol in one of the victims. Certainly that concentration of alcohol alone has been blamed for adverse driving performance. Practically nothing is known of the effects of combinations of alcohol and marijuana or any other drugs on driving. Intuition leads us to believe that the other drugs won't favorably improve the ability of the driver influenced by alcohol.

THC was found in the bloods of 9 of the 100 dead operators tested. In 6 of the 9 bloods, alcohol in sufficient concentration to influ-

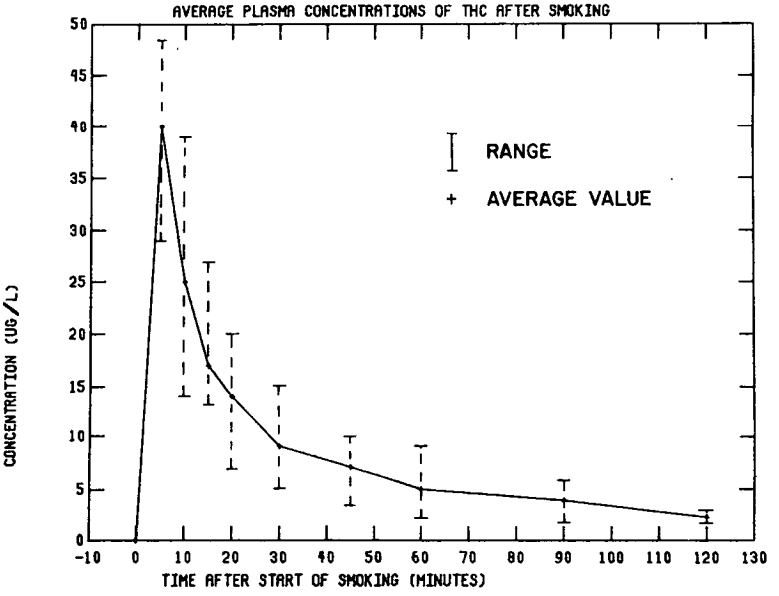

Figure 1. Each of 5 subjects smoked a marijuana cigarette that contained 9 mg of THC. It took 7 to 13 minutes to finish smoking.

TABLE 1. INCIDENCE OF THC IN 100 OPERATORS KILLED IN SINGLE VEHICLE CRASHES

A/R/S[a]	THC Ug/L	Ethanol %	Speed mph[b] Est./Limit	Time
25WM	18	0.11	50/55	6 am
34WM	3	0.18	100/55	11 pm
26WM	4	0.04	100/55	6 am[c]
18WM	8	0.30	60/30	9 pm
49BM	3	0.31	85/55	12 m[d]
22WM	5	0.09	80/35	2 am
18WM	7	0.17	60/55	10 Pm[e]
24WM	7	0.00	50/35	2 Pm
24WM	4	0.12	80/55	5 am

a. A/R/S = Age/Race/Sex. b. Est. = Estimated
c. Plus butalbital 0.06 mg/dL. d. Died in 1 hour.
e. Died in 25 minutes
Other drugs sought: Opiates, barbiturates, cocaine, amphetamines, phencyclidine (P.C.P.)

ence operation was also found. One blood which had a low concentration of alcohol also had a low concentration of butalbital. No opiate, amphetamine, or phencyclidine (P.C.P.) was found in any victim. Thus marijuana might have added to the effects of alcohol in 6 of the 100 cases (6%). Marijuana alone might have been a factor in 3 of 100 (3%). The incidence of alcohol in concentration greater than 0.09% was 62% (62 of 100). The number of drivers who had marijuana in their blood was very small compared to the number of those who had alcohol in their blood. Marijuana was not found in the bloods of 91% of the drivers tested.

It will be difficult to establish whether or not marijuana is a significant factor in traffic safety. The effects of marijuana smoking are subtle. It produces a pleasant state of relaxation, euphoria (a sense of well-being), altered perception of distance and time, impaired memory of recent events, and impaired physical coordination. This state lasts about an hour or two. Obviously some people will overindulge with marijuana as they do with alcohol and other drugs and their performance will suffer greatly. Are there many such people, will they try to drive, and will they have accidents? If marijuana has an adverse effect on operation, how much does it affect safety, for how long, and can the effect be correlated with THC blood concentrations? Is the marijuana-influenced operator more or less aggressive, apt to speed, likely to take fewer chances, able to compensate, etc.? Is driving adversely affected by marijuana in the same way that it is by alcohol and/or other drugs?

The presence of cannabinoids on the breath or in the saliva may be an indication that someone has smoked marijuana in the past few hours and that the oral cavity was directly exposed. Unless concentrations in the breath or saliva can be correlated with effect, these specimens will only be useful to show that marijuana has been smoked at some time recently. Cannabinoids persist in the urine for several days, thus positive urine specimens only identify marijuana users. It does not appear to be possible to develop an instrument for the detection and quantitation of marijuana that is as easy to use as alcohol breath testing equipment. Are such devices really necessary before it has been established that there is a significant risk associated with marijuana and driving?

It is difficult because of legal and logistic problems to obtain blood specimens from the general driving population so that the number of non-accident drivers who smoke marijuana and the concentration of cannabinoids in their blood can be determined. If marijuana is found in a small number of drivers killed in crashes, it would mean that it is not a significant problem regardless of what is found in the driving population. If a greater percentage of driving population had marijuana in their blood than the percentage in the crash group, would that mean that it is safer to drive after smoking marijuana? Probably the most meaningful answer concerning the effect of marijuana on driving will come from ana-

lyzing the bloods of operators killed in single vehicle crashes.

A recent Department of Transportation report to Congress emphasizes the need for information to "support arguments either for or against establishing marijuana as a high priority highway safety concern"(9).

More research should be undertaken before legislation and countermeasures are proposed to counteract a presumed problem of driving under the influence of marijuana. Until the time that marijuana is shown to be a significant problem, erratic operators may still be removed from the highway by arresting them for reckless driving.

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ACKNOWLEDGEMENTS

This study was supported in part by North Carolina Governor's Highway Safety Program. Project No. 80-08-03-C-308-2.

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The Role of Endorphins During Parturition

K. Csontos, M. Rust, and V. Höllt

Parturition in humans is generally associated with extreme physical and psychological stress under normal conditions. During pregnancy, parturition, and confinement several changes in the endocrinological homeostasis of the women take place. The controlling factors in the endocrinological regulation (the hypothalamic: hypophyseal peptide hormones) suggest a possible analgesic role of endorphins during delivery. Since β-endorphin and ACTH are located in the same precursor molecule (Mains et al. 1977) and are released simultaneously from the anterior pituitary in response to various stressful stimuli (Guillemin et al. 1977b), we have estimated ACTH levels as well as β-endorphin levels in the plasma of normal human female subjects undergoing labor and parturition.

METHODS

For the β-endorphin radioimmunoassay (RIA), antiserum was generated in rabbits using thyroglobulin-coupled synthetic human β-endorphin (β-h-endorphin) as the immunogen. The antiserum displayed a high avidity for human β-endorphin, (detection limit 4-6 fmoles/assay tube or 20-30 fmoles/ml plasma) (Höllt et al. 1975). Methionine-enkephalin, α and γ endorphin and several ACTH fragments displayed no cross reactivity. Human β-lipotropin (β-h-LPH), however, was recognized on an equimolar basis. 100 µl of undiluted plasma per 0.5 ml assay volume was assayed for immunoreactive β-endorphin. Synthetic β-endorphin was used as a standard and for iodination with I^{125} to provide the radioactive component of the assay.

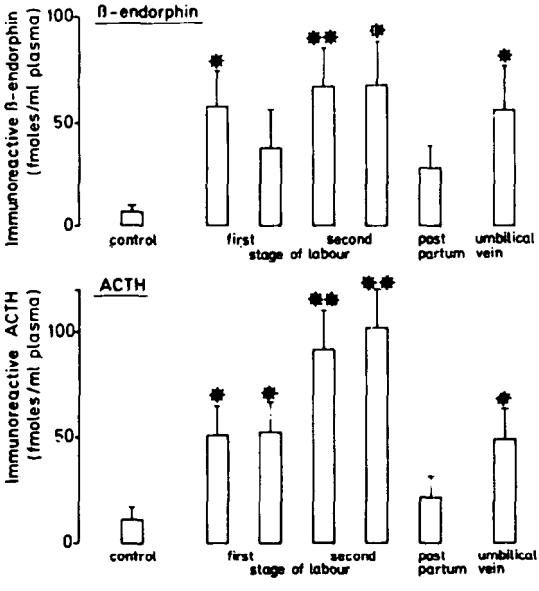
ACTH was assayed by a commercially available kit (adrenocorticotropic hormone RIA Kit-CEA SORIN, Salugia, Italy). In our laboratory we have established that this antiserum shows no cross-reactivity to human β-endorphin, β-LPH and α-MSH. 100 µl of undiluted

plasma per 0.5 ml assay volume was assayed for immuno-reactive ACTH. In order to separate the immunoreactive peptides, β-endorphin and β-LPH, 20 ml plasma aliquots were extracted by the silicic acid (50 mg/ml plasma) and subjected to gel chromatography on a 09 x 85 cm analytical column containing Sephadex G-50. The separate lobes of the pituitary of a 22-week-old stillborn fetus were extracted with 0.1N HCl and also subjected to gel chromatography. 10 ml venous blood samples from the mother were collected in the different stages of labor and parturition and one day post partum, furthermore, from the umbilical artery and vein of the newborn. Venous blood samples were withdrawn from 12 mothers undergoing parturition with segmental epidural anesthesia, from pregnant women during oxytocin-induced labor, registered labor without subsequent parturition, from mothers during and after nursing and, from non-pregnant women during several stages of diagnostic dilatation and curettages.

RESULTS

Fig. 1 illustrates that plasma levels of both immunoreactive β-endorphin and ACTH in pregnant women and their neonates are significantly elevated above those seen in non-pregnant women. One day post partum the elevated peptide levels in maternal plasma seen during labor had significantly decreased, and there was no marked difference from normal control levels. There was a slight decrease

Figure 1



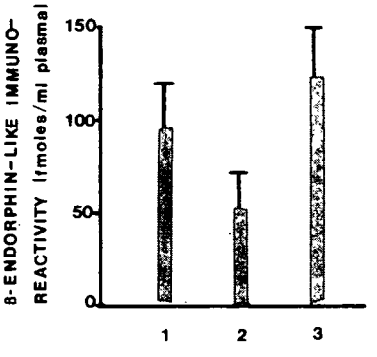
*Immunoreactive β-endorphin (A) and ACTH (B) in the plasma of controls and in several stages of labor and in umbilical vein. Astericks indicate significant differences between control and other values (p=<0.05 *; p<0.01 **)*

in plasma levels of immunoreactive ß-endorphin in the moment of labor intervals as compared to the second stage of labor. Plasma levels of immunoreactive ACTH were found to be significantly increased in the second stage of labor as compared to the first stage. When compared to nonpregnant women, elevated plasma levels of both immunoreactive β-endorphin and ACTH were found in the umbilical vein of the new-borns.

To investigate the possible releasing activity of the routinely used oxytocin infusion, labors were induced and registered in 8 women in the 42nd week of pregnancy by a continuous infusion of orathin (Fig. 2). Venous blood samples were collected before, during and after the 20 min. long infusion period. There was no statistically significant increase in the immunoreactive β-endorphin (β-ELIR) during the induced labors. There was a slight decrease in the β-ELIR in the plasma. Therefore, routinely administered oxytocin infusion does not seem to be responsible for the increased endorphin release.

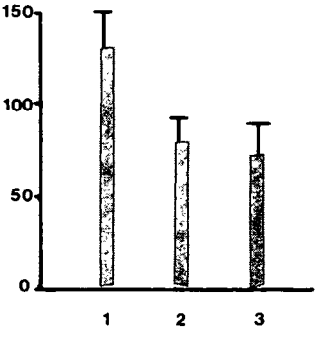
The highest levels of β-endorphin/β-LPH in maternal plasma were observed immediately after delivery and probably reflect the extreme physiological stress of the birth process (Fig. 3). No difference between umbilical, venous and arterial β-endorphin con-

Figure 2



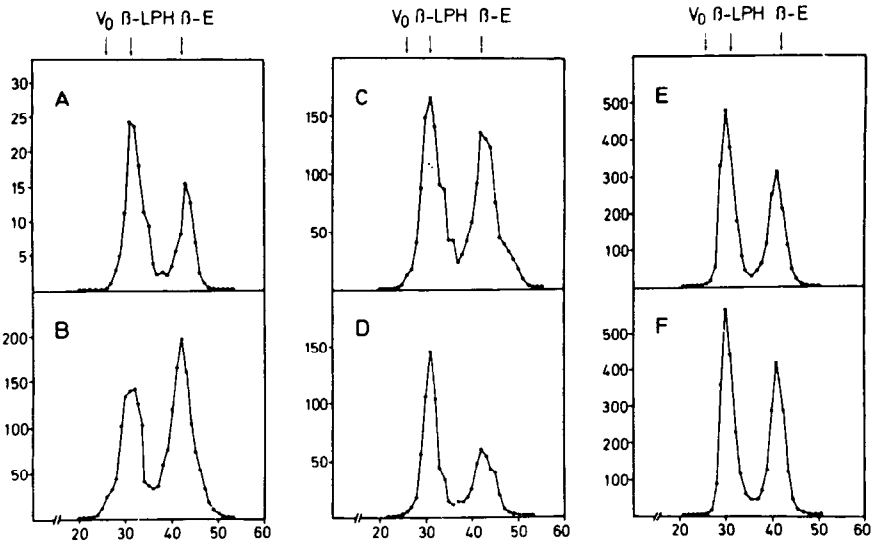
Immunoreactive β-endorphin in plasma of women before (1), during (2) and 1 hour after (3) oxytocin infusion in induced labor

Figure 3



Immunoreactive β-endorphin in maternal plasma (1), umbilical venous (2) and arterial (3) plasma immediately after partition

Figure 4

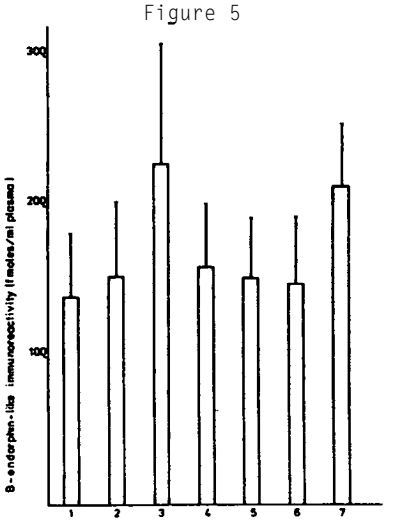


Separation of immunoreactive β-endorphin into β-lipotropin (β-LPH) and β-endorphin (β-E) by gel filtration on Sephadex G-50 after silicic acid extraction from plasma. A= 10 non-pregnant women B= 10 pregnant women in second stage of labor, C= umbilical vein, D= umbilical artery of 20 neonates, E= anterior lobe of pituitary, F= intermediate/posterior lobe of 22-week-old fetus. Ordinate is β-endorphin-like immunoreactivity in fmoles/fraction.

tent could be detected. In Fig. 4, the chromatographic separation of β-ELIR into its components in plasma and tissue extracts of humans is shown. The figure illustrates the elution profiles of immunoreactive components of extracts of 30 ml plasma samples pooled from non-pregnant women (A), from pregnant women during second stage labor (B), from umbilical vein plasma (C), and from umbilical artery plasma (D). In all cases the immunoreactive peptides eluted from the columns showed fractions corresponding to both β-h-LPH and β-h-endorphin. With the exception of the maternal plasma during labor, β-h-LPH appears to be the predominant peptide in plasma. The fetal pituitary anterior and intermediate/posterior lobes also contain equal amounts of both peptides.

Segmental epidural anesthesia during spontaneous delivery does not seem to have an influence to the peptide plasma levels (Fig. 5). High levels with little fluctuation were detected during the whole observation period. In pregnant women plasma β-endorphin content was not influenced by the mechanical stimulus of dilation and curettage (Fig. 6). Elevated level of β-endorpin in the plasma

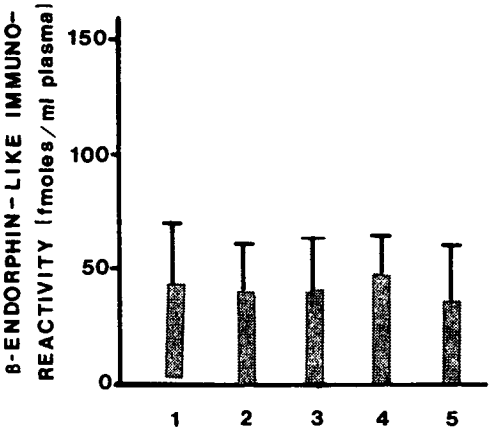
Figure 5



Immunoreactive β-endorphin in the plasma of women giving birth under segmental epidural anesthesia. Plasma withdrawn at first stages of labor (1-3), second stage of labor (4,5), umbilical vein at delivery (6) and 1 day post partum (7).

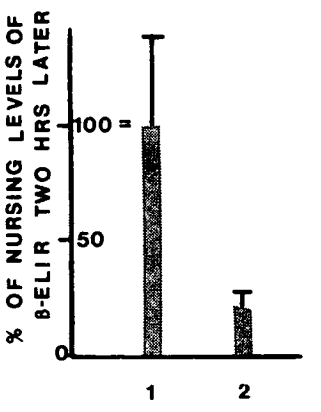
during nursing was detected (Fig. 7). One hour after nursing only 12% of the peptide level during nursing was observed in the plasma of a mother 6 days after parturition.

Figure 6



Immunoreactive β-endorphin in plasma of non-pregnant women during dilatation and curettage

Figure 7



Immunoreactive β-endorphin in maternal plasma during (1) and after (2) nursing

DISCUSSION

In comparison to non-pregnant female controls, significantly elevated plasma levels of both β-endorphin and β-LPH in maternal and neonate plasma could be detected during labor and parturition. ACTH levels rise also during parturition, reaching maximums in the second stage of parturition. Our results confirm those of Kauppila (1974). Between the phases of uterine contraction and dilatation no significant difference in the ACTH levels was detected, whereas there was such a difference in the content of β-endorphin immunoreactive materials. A faster metabolic clearance rate for β-LPH than ACTH has been reported (Liotta et al. 1978).

Immediately after parturition very high levels of β-endorphin/a-LPH were also observed in plasma of the infant, although significantly lower than in the maternal plasma. Possible sources for these elevated peptide levels in the circulatory system of the neonate are the maternal plasma, the placenta, (which has recently been shown to contain high levels of β-endorphin/β-LPH (Nakai et al. 1978) or the fetal pituitary (Nakao et al. 1978). If the major source of β-endorphin/β-LPH in the neonate plasma is the maternal plasma, placental transfer by diffusion would depend largely on a maternal-fetal concentration gradient and a tendency for equalization of the respective concentrations should be noticed. But it is well known that, when a drug has a molecular weight above 600, placental transfer by diffusion does not occur. Since it has been shown that ACTH (molecular weight 4500) can not readily penetrate the placental barrier, it is unlikely that peptides such as β-endorphin (molecular weight about 3500) or β-LPH (molecular weight about 1000) could cross it to a major extent.

If the maternal plasma or the placenta were the major source of β-endorphin and B-LPH, higher concentrations of the peptides should be expected in the umbilical vein than in the umbilical artery. Although significant secretion of β-endorphin/β-LPH from the placenta cannot be excluded, our findings indicate that at least the most of the peptides in the neonate plasma are secreted by the neonate pituitary.

In view of the analgesic properties of opioids, one is tempted to speculate about a possible physiological role of β-endorphin in human labor. The analgesic properties of β-endorphin are well known (Guillemin et al. 1977a). Thus an increase of this peptide might help in rendering mother and infant less sensitive to the pain of labor and parturition. It should be realized, however, that the highest levels of β-endorphin measured in maternal and fetal plasma are very low (in the range of 40 to 150 fmole/ml or 40×10^{-11} to 1.5 x $10\text{-}10_M$). Even if one assumes that the infant has not yet a fully developed blood brain barrier and drugs like morphine penetrate the fetal nervous tissue more easily than its adult counterpart, the amounts of plasma β-endorphin appear too low to cause any analgesic effect in test systems routinely used for analgesic sensitivity. However, no exact data are available about the pain-sensitivity of women undergoing parturition and their neonates.

One can not exclude that at a decreased pain threshold these concentrations of β-endorphin could be analgesically active in mother or infant. Since functionally active opiate receptors are already present in early stages of the fetal development (Cox and Pert 1976) ananalgesic action of endorphins in the fetal compartment at parturition can be assumed.

Elimination of the painful component of parturition by segmental epidural-anesthesia seems to have no effect on the elevated β-endorphin levels in the plasma. The emotional stress still remains unaffected. In this case, the physical pain does not seem to be responsible for the β-endorphin release. The mechanical stimulation of the cervix by dilatation and the irritation of the uterus by curettages induces also no endorphin release, as shown by our results.

The interaction of the endocrine system with opiates has been studied extensively. The synthesis and secretion of several pituitary hormones (ACTH, GH, prolactin) are affected by the specific action of both exogenous and endogenous opiates (Fishman 1977). In our investigations the opiate-induced release of prolactin by PIF synthesis inhibition is of great interest. This regulatory step occurs on the hypothalamic level. Prolactin has an important role in inducing labor and thereby in initiation of parturition. We can assume that the β-endorphin modifies the release of pituitary hormones during and after birth. Our findings of highly elevated β-endorphin levels in plasma of mothers during nursing indicate a pronounced interaction between the endocrine system and the endogenous opiates.

SUMMARY

The concomitant in vivo release of immunoreactive ACTH and β-endorphin was investigated by measuring the plasma levels of both peptides in the plasma collected during labor and parturition of female human subjects. Maternal and fetal β-endorphin circulation was investigated by estimating the plasma levels in umbilical vein and artery and comparing them with the maternal plasma content of the peptide. The peptides β-LPH and β-endorphin (which both react with the β-endorphin antiserum) were separated chromatographically on Sephadex G-50.

In the first, and particularly the second stages of labor, levels of both ACTH and β-endorphin were significantly elevated. The β-endorphin-like innnunoreactivity was also elevated in the umbilical vein and artery, although these values were not as high as in the maternal vein.

Neither oxytocin nor the mechanical stress produced by dilatation and curettage played a large role in releasing ACTH and β-endorphin. The normal pathways of releasing pituitary trophic hormones (disinhibition of inhibitory control of releasing factors in the hypothalamus) must be assumed for the mothers, while fetal production of both β-endorphin and β-LPH was demonstrated.

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Regulation of Alcohol, Tobacco, and Other Drugs: The Agenda for Law Reform

R. J. Bonnie

INTRODUCTION: THE AGENDA FOR LAW REFORM

Let me begin by endorsing what I will call the public health model of drug regulation. The model has two predicates. The first is that it is desirable for government to aim to prevent and minimize those patterns of use--of any substance--which can result in impairment of health and/or normal behavioral functioning. Little dissent is likely to be raised on this point. However, the major implications of the public health model derive from its second predicate--the view that it is legitimate for government to discourage and attempt to minimize any consumption of any potentially harmful substance as a means of preventing the patterns of use that can result in behavioral impairment and/or adverse effects on health. This second notion is empirically rooted in what the alcohol literature refers to as the distribution hypothesis. According to this hypothesis, the prevalence of alcohol problems in a society is linked to the amount of alcohol consumed in that society, and such problems can accordingly be reduced by reducing aggregate (or per capita) consumption.

Insofar as our current drug policy is rooted in the logic of public health (rather than a moral authoritarianism), its very foundation is the distribution hypothesis. Many hard questions can be raised about the policy implications of the distribution hypothesis, but I do not want to dwell on them now. I would just like to assume that this is a legitimate way of thinking about drug abuse control. With this basic assumption in mind, I want to focus my attention on how the law is best used in the effort to implement a policy which is built on the public health model.

The critics of marijuana prohibition never fail to call attention to the disparate governmental approaches to alcohol and tobacco. They have consistently offered the so-called alcohol model as a useful guide for enlightened marijuana control. Yet I think we will all agree that this nation's experience with the alcohol model is nothing to be proud of, certainly as it is currently practiced. To the contrary, the laws now regulating alcohol tend to be wholly inconsistent with the logic of the public health model, reflecting instead what I would call "affirmative libertarianism"--that is, the current regulatory system often appears to be designed to facilitate and encourage the use of alcohol. The case of tobacco is even more disturbing since the public health model has supposedly been the basis for our policy since the mid 1960's when the Surgeon General's report was issued (1964) and the first Public Health and Smoking Act was passed (1965). Yet, despite its rhetoric, government has taken only a few very tentative steps to implement a public health approach toward tobacco use.

The National Commission on Marihuana and Drug Abuse, of which I was Associate Director, is remembered best, whether fondly or not, for its recommendation that marijuana use be decriminalized (National Commission, 1972). But what may be more important, I think, is the Commission's unqualified endorsement of the public health model. Not only did the Commission say that use of marijuana and other illicit drugs should be discouraged, but it also took the position that nonmedical use of all drugs, including alcohol and tobacco, should be discouraged as well. As this may suggest, the Marihuana Commission's Report is actually a very conservative document.

I thought when the Commission issued its final report--and I still believe--that its most significant contribution lies in its effort to lay the groundwork for a more coherent and sensible legal policy toward all drugs--marijuana and other illicit drugs as well as alcohol and tobacco. It should not be assumed, the Commission emphasized, that the mere lawfulness of a behavior, such as the use of alcohol and tobacco, means that the government approves the behavior or is indifferent to it. In fact, the Commission said, the government should take affirmative action to erase any such impressions and to influence even lawful behavior in ways which would promote and protect the public health. Laissez faire may well be a sound policy if it is rooted in an ideological commitment to libertarianism, but it is hardly a policy at all when government has simply abandoned the field to the forces which have no interest in the public health or welfare.

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On the other hand, the Commission also emphasized that when government takes a stance of disapproval, even strong disapproval, it does not follow that the behavior must be prohibited with all the coercive power of the law. In short, the Commission said, the public health model can be implemented by a variety of legal strategies, and the assessment of the benefit and costs of the various legal options requires a more subtle analysis than is customarily offered.

These observations lead to a two-part agenda for law reform. First, we need to develop creative regulatory strategies--I use the word "regulatory" in a narrow sense here, as opposed to "prohibitory"--for the implementation of discouragement policies. How can the law be used most wisely and effectively to implement a public health ideology towards tobacco and alcohol use? (My point is not limited, by the way, to alcohol and tobacco use; similar questions can be raised with regard to automobile safety, for example.) What steps should be taken to qualify what I regard as the mindless libertarianism of our alcohol and tobacco policy?

The second item on the law reform agenda is to fix the appropriate role of the criminal law in implementing a policy which aims to minimize the use of illicit drugs. Even if a prohibitory model is adopted--rather than a regulatory model which legitimizes availability--it need not be an intolerant and oppressive policy. Prohibition of commercial, nonmedical availability may be a sensible policy in many respects, but it does not follow that the user who chooses to ignore the prescribed norms, and who is able to obtain the drug despite society's best efforts to keep it from him, should be punished. What we need, the Commission said, is discouragement without criminalization. The Commission elaborated on this fundamental point:

> In determining conditions of availability for psychoactive substances, policymakers should err in the direction of too much restriction rather than too little. Philosophical and constitutional concerns for individual privacy and freedom are touched only indirectly by society's legitimate efforts to resist the adverse consequences of drug availability. Therefore a presumption exists in favor of restriction and decisions limiting availabil- may well be defended on speculative grounds. "What would happen if there were widespread availability?" is a perfectly valid inquiry. Too often, however, policymakers have taken the same perspective and employed a similar line of reasoning in connection with an en-

> tirely distinct policy decision. That is whether and under what circumstances society should intervene in the life of an individual who has chosen to consume a substance outside the legal channels of availability. Here for philosophical, constitutional and many practical reasons the presumption in favor of control should be reversed. The policymaking perspective must emphasize personal freedom rather than the protection of society. In a free society, the state is obliged to justify restraint on individual liberty, and this justification must rest on facts, not on speculation. (National Commission, 1973, p. 242-43)

The Commission also went on to point out this society's ambivalent attitudes toward drug use, the relative ineffectiveness of the possession penalty as a deterrent to use, and the high social cost of its enforcement, and concluded that the criminal law is not a necessary symbol for a discouragement policy. Yet, the Commission cautioned, "until society develops a replacement symbol and other institutions assume their share of responsibility for control and discouragement, [the criminal law] may well be a necessary codification of public policy. Unfortunately, sixty years of coercive policy have so exaggerated the symbolic importance of the criminal law that it has become interwoven with social attitudes regarding drug use. Removing it suddenly would connote a change in values rather than perhaps a shift in emphasis." (Id., p.255-56)

The Commission's discomfort about the situation is apparent:

> Perpetuating the criminal law principally through its symbolism does not comport well with the fundamental purposes of the rule of law. The Commission is strongly of the opinion, however, that policymakers cannot abruptly displace criminal law as a central support for control of drug-using behavior. The common reaction of those opposed to the Commission's recommendations to remove the criminal sanction from possession of marijuana for personal use illustrates the difficulty of rearranging even part of the structure. We observed in our first Report that a legal policy designed to curtail the availability of cannabis could no more be construed as neutrality toward or approval of marijuana use than a similar legal scheme

> employed during alcohol prohibition. (During alcohol prohibition possession for personal use was an offense in only five states.) Nevertheless, there has been a chorus of objections that withdrawal of the criminal sanctions would signify approval of use and encourage more consumption of the drug. (Id., p. 256)

The Commission went on to reaffirm its view that the criminal proscription of marijuana use is self-defeating as a means of implementing a discouragement policy. But the Commission was equivocal on the use of the criminal law to proscribe and punish possession of other drugs. "In the long run," the Commission said, "a measure of success of this nation's drug policy will be how much we have been able to disengage the criminal law from concern with consumption. As long as the legality of consuming legal drugs is a sign of approval and the criminality of using prohibited drugs is the major symbol of disapproval, the law will continue to bear the sole burden of fulfilling public policy of discouragement and most certainly will bear it badly." (Id.). In the short run, however, the Commission concluded--and until replacement symbols are developed--the possession penalty should probably remain in force for other drugs. Even then, the Commission went on to say, enforcement efforts should be selective and carefully chosen in order to minimize the adverse effects of criminal intervention.

This, then, was the two-part agenda for law reform in 1973. The question that I would like to address today is where we are seven years later. I will take up each of these two items in turn--(1) regulatory implementation of discouragement strategies, and (2) "discouragement without criminalization" under prohibitory policies. Before going into the details, let me note in passing that I am more sanguine about the likelihood of progress in the area of alcohol and tobacco regulation than in the area of drug abuse control. In fact, I will call attention to several recent signs of regression in drug policy.

IMPLEMENTING DISCOURAGEMENT POLICIES: REGULATION OF ALCOHOL AND TOBACCO

Let me now take up tobacco and alcohol regulation. Events during the last several years suggest that considerable momentum is building for rethinking our legal policies toward alcohol and tobacco. These policies have become one of the targets of what the Surgeon General has called the "second public health revolution." The recruits in this revolution carry a banner sounding

the call for "Primary Prevention," and their manifestos emphasize the need to engineer changes in collective lifestyle as an essential component of the new public health initiatives. The effort to prevent disease and other health problems, it is said, must include measures designed to discourage unhealthy personal choices and to promote healthy ones. The target behaviors of this new public health revolution--what I have elsewhere called the "new paternalism" (Bonnie, 1978) --always include alcohol abuse, tobacco smoking and poor eating habits. Proponents of lifestyle modification strategies also always single out pregnant women and adolescents as target populations in need of special emphasis.

My sympathies lie with the "new paternalism." I even support the use of regulatory measures . . . but only if they appear to be essential components of an effective strategy for discouraging the use of tobacco and for reducing the adverse health and social consequences of alcohol abuse. In saying this, I stand somewhere between the "health promoters" who want only to persuade, and the most vocal "preventors" who seem to want health at almost any cost.

Organized social action aiming to generate mass changes in lifestyle can, of course, be limited to health education and to other efforts to influence collective behavior in desired directions by reshaping attitudes and social norms. Many contemporary advocates of lifestyle modification strategies say that they want only to promote the values of health, and therefore to orchestrate voluntary behavioral change. Thus, they accent the positive and frequently disclaim any interest in seeking more potent regulatory initiatives. Yet I am convinced that the new "public health revolution" will fail miserably to produce any measurable result unless its leaders are prepared to sponsor regulatory initiatives. This is especially, true in connection with alcohol and tobacco use.

Tobacco Policy

Let us take a quick look at the chronology of the recent Federal anti-smoking initiative. In early 1978, Secretary Califano launched the anti-smoking campaign with considerable fanfare, emphasizing the desirability of curbing smoking as a means of reducing chronic disease. Despite the speculation that Secretary Califano's dismissal was attributable, in part, to the political fall-out from the anti-smoking campaign, Secretary Harris promised to continue it. A year later, in 1979, Dr. Richmond issued the Surgeon General's Report on Smoking and Health, a 15-year follow-up to

the famous 1964 Report. The smoking issue also received considerable attention in the Surgeon General's Report, entitled Healthy People, launching the Department's health promotion, disease prevention initiative. (DHEW, 1979)

But, let us ask, what is the goal of these Federal initiatives? Listen to what an HEW Task Force on prevention had to say about this in September 1978:

> There are a number of significant gaps in the Department's work on smoking: considerable knowledge has been developed about the health effects of smoking, but too little about the behavioral factors associated with smoking. . . . The Department has not sponsored a strong systematic campaign to provide information about the dangers of smoking until January 11, 1978, when Secretary Califano announced a major new smoking reduction effort by HEW to increase education, research and regulation. The purpose of this renewed commitment is to provide information to permit American citizens to make a genuinely free choice about smoking and their own health. (DHEW, 1978, p. 109-10) [Emphasis added.]

Is that really the goal--to promote a genuinely "free choice"? Or is the nation's goal to promote the right choice--not smoking--and to discourage and prevent the wrong choice--smoking?

The Department of HHS will soon announce its long-awaited specific Prevention Goals for the 1980's. These Goals have been the product of a year-long process involving 15 separate working groups producing quantifiable objectives in 15 specific areas. One was on smoking. Here the goal is clearly stated:

> By 1990, the proportion of adult women who smoke should be reduced to below 25 percent. (In 1979, the share was 30 percent.)
>
> By 1990, the proportion of adult men who smoke should be reduced to below 25 percent. (In 1979, the share was 38 percent.)
>
> By 1990, the proportion of 12 to 18 year old girls who smoke should be reduced to below 6 percent. (In 1979, the share was 13 percent.)
>
> By 1990, the proportion of 12 to 18 year old

boys who smoke should be reduced to below 6 percent. (In 1979, the share was 11 percent.) (DHHS 1980)

Once we acknowledge that reduced smoking is the goal, we must confront the crucial question: How are we going to go about achieving this goal, especially in the face of data which suggest that cigarette smoking is on the increase among teenagers and women? Specific measures are recommended in the prevention goals document, including stronger health warnings, bans on smoking in places of public accommodation, and insurance premiums which differentiate between people who smoke and those who do not. But note that the industry remains essentially untouched by these recommendations. Nothing is said about the conditions of availability, even though cigarettes are promiscuously available in our society, especially to the young. One need not walk very far in any part of this country in order to find a vending machine, a convenience store or another retail outlet for cigarettes. Meanwhile, the industry's print advertising budgets continue to increase, and the real price of cigarettes continues to fall, relative to disposable income, in most parts of the country.

I simply do not believe that these smoking reduction goals can be achieved while the conditions of availability are so carefully ignored. Again, without endorsing any particular approach to regulatory policy, I am convinced that serious consideration must be given to possible regulatory initiatives as part of any major prevention program.

To summarize, the Nation's tobacco policy is moving in the right direction, but its focus should be clarified and its pace increased. Let me make three specific recommendations in this regard.

First, the objective of national tobacco policy should be clearly and unequivocally stated. The goal is not, as is sometimes said, to facilitate informed, or genuinely free, personal choice. Instead, the goal is to reduce cigarette consumption in the United States, to reduce the number of people who smoke and how often they smoke. The objective, simply put, is to discourage consumption.

Secondly, Federal programming for prevention of cigarette smoking should not be limited to the initiatives of the Office of Smoking and Health. Nor should it be subsumed within the generalized mandate of the reorganized Center for Disease Control. Instead, HHS should designate an identifiable "lead agency" for prevention of tobacco-smoking, with a specific mandate.

I do not have a concrete proposal to make, but one possibility which seems to make conceptual sense--whether it makes bureaucratic sense or not--would be to give NIDA programmatic responsibility for prevention of cigarette smoking and for implementing discouragement policies with regard to use of tobacco as well as the so-called illicit drugs.

Thirdly, the Federal Government should work with the States to sponsor demonstration programs which aim to reduce smoking by regulating the conditions of availability. Let me emphasize that I am not claiming that the case can now be made, empirically, for various types of regulatory initiatives. But I am arguing that, despite all the fanfare about cigarette smoking prevention, no systematic attention is now being given to this area. Let me take the example of using taxing policy as a means of reducing consumption by driving the price up. Some available data suggest that a significant price increase would reduce aggregate consumption. The Federal Government should stand ready to assist States who want to find out. Another possibility is to reduce the accessibility of tobacco to the consumer. Our drug abuse policies, and some State ABC regulations, are predicated on the assumption that aggregate consumption can be reduced and contained by making access more costly and inconvenient. For drugs, we drive the distribution system underground. For alcohol, some States curtail the number of retail outlets. Meanwhile tobacco is available everywhere, even to the young. We say it is illegal to distribute tobacco to people under age, and yet vending machines can be found in every building in the universe. A vending machine ban in some locality which is committed to the "new paternalism" would provide an opportunity to study the impact of such a ban on consumption patterns, especially among the underage.

Alcohol Policy

Recent concern about the fetal alcohol syndrome has stimulated considerable interest in health warning labels for alcoholic beverages. The leadership of both the FDA and NIAAA are on record favoring such warnings, although the Bureau of Alcohol,. Tobacco and Firearms, which apparently has jurisdiction over the matter, has been slow to act. In September of 1979, Senator Thurmond of, South Carolina proposed to amend the Comprehensive Alcohol Abuse and Alcohol Prevention and Rehabilitation Act to require the following warning on any beverage container having more than 24 percent alcohol: "Caution, Consumption of Alcoholic Beverages may be Hazardous to your Health, May be Habit-Forming and May Cause Serious Birth Defects when Con-

sumed During Pregnancy." Senator Huddleston of Kentucky argued that such a mandatory warning would be somewhat precipitous in the absence of definitive data concerning the effectiveness of such warnings when compared with other devices such as public information campaigns. Although Senator Huddleston's argument did not carry the day in the Senate--which passed a warning provision--Senator Thurmond was persuaded to water it down. As passed by the Senate the warning would have stated: "Consumption of Alcoholic Beverages May Be Hazardous To Your Health." Obviously, this is the same warning required for cigarette packages and advertising since 1965; it says nothing about alcohol dependence and nothing about the risk of fetal defects.

Although the House omitted any warning provision from its bill, the House-Senate conferees agreed on the inevitable compromise--they directed the Secretaries of HEW and Treasury to report to the Congress and the President by June 1, 1980 concerning the health hazards associated with alcohol use and the actions which should be taken by the Federal Government to inform the general public of such health hazards. (I understand that the deadline has since been extended.)

During the Senate debate on the warning provision, Senator Thurmond repeatedly insisted that the purpose of the alcohol warning was not to regulate people's lives but simply to provide the consumer with information. Similarly, the Director of NIAAA testified that he viewed the warning labels as one of the many forms of public education, not as a regulation for control:

> Such warnings may not have an immediate or measurable impact on existing patterns of consumption. This does not relieve us of our obligation to inform the public of a scientifically established health hazard. I suppose that various portions of the public may well be unaware of the risks that are associated with alcohol use especially by pregnant women and I suppose in this sense package warnings may well be a useful supplement to media information campaigns and educational programs.

But if this were the proponents' only purpose in seeking such warnings, I think the industry might legitimately claim--as its spokesman, Senator Huddleston, did on the Senate floor--that package warnings are too inspecific to provide the consumer with the necessary information, and that there might be better ways of accomplishing this objective. The simple fact is that the industry resists the labeling requirement precisely because it fears that one consequence would be

reduced consumption. It fears that the warning is designed not to "promote informed choice" but rather to push people in the direction of making the choice that the government would prefer.

Again, the problem is that the Federal Government has not yet come to terms with the need to formulate an alcohol consumption policy. Since the repeal of Prohibition, the goal of the nation's alcohol policy, if there has been one at all, has surely not been to discourage consumption. Indeed, the National Government has carefully left the matter to State and local prerogatives. Meanwhile, the trend in Alcohol Beverage control has been to liberalize the conditions of access. In fact, State ABC officials seem to assume that the 21st Amendment not only repealed the Volstead Act but also established the illegitimacy of any governmental effort to try to influence consumption.

The recent NIAAA Forward Plan for 1979-1983 minces no words on the need for Federal leadership in planning and implementing a Federal prevention effort and for a concentrated attempt "to change social policy as it defines alcohol use in the United States." To put it succinctly, NIAAA, at least in 1978, did propose to implement a national consumption policy. Even more significant is the content of that policy. One of the Institute's major goals over the next five years, it said, would be to stabilize per capita consumption of alcoholic beverages at the current level of 2.7 gallons annually. And here the Forward Plan explicitly endorses the so-called distribution hypothesis:

> There is strong evidence that as consumption rises, so do primary and secondary problems related to the use of alcohol. Since the trend in this country during the last decade has been toward ever increasing total consumption, a major effort is required to stabilize the increase which in view of the population increase will in reality result in a reduction of per capital consumption. (NIAAA, 1978, p. 9)

Obviously, NIAAA's impending prevention initiative is a significant departure from the national Government's hands-off posture toward alcohol consumption which has been in effect since the repeal of Prohibition. Moreover, it will be moving against the grain of public opinion, will endanger vested economic interests and will reverse current trends in ABC law reform. For these reasons, the NIAAA Forward Plan listed among its primary objectives the need "to work with the States to consider the public health consequences of existing ABC

laws." This year the NIAAA prevention plan characterizes research in this area as a major priority. (ADAMHA, 1980)

I applaud these efforts by NIAAA to overcome the momentum of blind libertarianism. If we are ever to have a fighting chance of reducing alcohol problems, we cannot afford to ignore the norms of drinking behavior and the relevance of the conditions under which alcohol is available. By saying this, however, let me emphasize that I am not endorsing any particular regulatory approach; I am only emphasizing that some attention to the regulatory system must be an essential ingredient of a revived public health approach to alcohol problem prevention.

DISCOURAGEMENT WITHOUT CRIMINALIZATION: ILLICIT DRUGS

I am less sanguine about recent trends in the area of illicit drug use--where the nation has adopted a prohibitory model toward availability. Considerable progress was made in the mid-1970's in curbing the oppressive excesses of the prohibition policy. Eleven States decriminalized marijuana use between 1973 and 1978. A national treatment network was put in place, and strongly supported, by the Federal Government, both in principle and in terms of budgetary policy. Also enforcement priorities were generally rearranged by the Federal enforcement officials as well as by State and local police--toward supply and away from prosecuting users. I generally thought we were in the process of institutionalizing a policy of tolerant discouragement, as the Commission had recommended--an approach aiming to provide help where needed and to avoid intervention otherwise.

I am not so sure any more. Unfortunately, the forces of fear and authoritarianism have reemerged during the last several years. The foot soldiers of a renewed policy of oppression are the 400 parent groups which have emerged all over the country. However well intentioned they are, I am concerned that they are doing the cause of enlightened drug abuse prevention a considerable disservice.

Their central message is relatively simple, and I have heard it many times: "If you are concerned about our children and want to discourage them from using drugs, you must be against decriminalization and in favor of bans against head shops, and paraphernalia distribution. Unless you support coercion, in short, you are in favor of drug use."

But this is wrong and wrongheaded.

I, too, am personally troubled by recent increases in illicit drug use by our teenagers. I, too, am concerned about our failure to develop effective and meaningful approaches to discouraging teenagers from using tobacco, alcohol and marijuana, as well as other drugs. But I also know that criminal sanctions for possession of marijuana make no measurable contribution to our discouragement policy and cause a lot of harm along the way. All the available data indicate clearly that consumption patterns are substantially the same in decriminalized and nondecriminalized jurisdictions. Thus, the argument for retaining the criminal sanction is essentially a symbolic one, and, as the Commission noted as long ago as 1972, we pay an extraordinarily high price for this ounce of symbolism.

I also know that the "head shop" bans--on advertising and selling commodities whose "primary intended use" is to facilitate the use of illicit drugs--are unconstitutional, as virtually every court which has confronted the question has concluded. As is the case with the anti-decriminalization movement, the proponents of these head shop bans really do not expect to suppress consumption of illicit drugs through these ordinances. Instead, I think the argument is primarily a symbolic one.

The paraphernalia bans are really efforts at message regulation. They serve the same purpose as proposed bans on advertising by the liquor and tobacco industries. That is to say, they are designed to purge the environment of those messages which are thought to encourage the disapproved behavior--here the use of illicit drugs. But I need not remind you that the cultural environment is replete with messages which can be seen or interpreted as encouraging or "glorifying" the use of illicit drugs. Styles of dress and music, and the attitudes and behavior portrayed in contemporary movies and literature reflect current social realities--and the undeniable truth is that drug use is widespread in Western culture. I am reminded in this connection of the extraordinary scenes concerning use of opium during the late 19th century in the movie called "McCabe and Mrs. Miller."

I care nothing for the economic rights of the purveyors of paraphernalia, any more than I care for the economic rights of those who make and distribute X-rated movies or pornographic magazines, but I do care for their freedom of expression.

The point is this: a policy of "discouragement without criminalization" is responsive to the behavioral realities of drug use: the factors which influence decisions to use or continue to use these drugs--or which

affect the intensity or frequency with which they are used--are too varied, and too subtle to be effectively offset or neutralized by the blunt hand of authority, especially the coercive hand of the criminal law.

However much we are committed to the public health ideology of drug abuse control, we should remember that health and conformity to majoritarian norms are not universally regarded as the supreme values in our society. I have rejected the blind libertarianism which, in my opinion, obstructs rational regulation of alcohol and tobacco. But I must now also reaffirm my distaste for the blind paternalism which cares not for liberty at all.

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Progress Reports

Annual Report: Biological Evaluation of Compounds for Their Dependence Liability. IV. Drug Testing Program of the Committee on Problems of Drug Dependence, Inc. (1980)

A. E. Jacobson

INITIAL PROCEDURE

The procedures used to evaluate compounds for their dependence liability, under the auspices of the Committee on Problems of Drug Dependence, Inc., have changed, and are becoming formalized at the Medical College of Virginia (MCV) and the University of Michigan (UM). The roles played in the testing program by the National Institute of Drug Abuse (NIDA), and the National Institutes of Health (NIH) will be mentioned.

Compounds submitted to me are accepted for evaluation in our initial screens if they are accompanied by data relating to the identity and purity of the compound, and if the submitter is fully aware of our policy on the release of obtained data (within 3 years of submission). To remain in compliance with the Good Laboratory Practice Regulations of the FDA, we request thin layer chromatographic (tlc) and infrared (ir) spectroscopic data. The tlc is repeated at, for example, MCV before that group initiates its work; the ir spectrum may be repeated at NIH. The compound is initially examined at NIH for antinociceptive activity in the hot plate and, occasionally, the Nilsen assay. The obtained data are included in the reports submitted by MCV and UM. The hot plate assay data are utilized to obtain a starting dose for the single dose suppression (SDS) test at MCV or UM. Perhaps 10 percent of the submitted compounds are evaluated at both MCV and UM in SDS, for various reasons.

BIOLOGICAL EVALUATION -

The submitted sample is distributed to both groups for testing. If MCV runs the SDS assay, UM will obtain biochemical data (binding affinity to opiate receptors in rat brain homogenates, electrically stimulated guinea pig ileum and vas deferens assays). If UM runs the initial SDS test, MCV will run rodent antinociceptive tests (tail flick (TF) and phenylquinone writhing (PPQ)) and the tail flick antagonist assay (TFA). I

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combine, and compare, these reports and send a copy to the submitter of the compound. Biochemical data, of course, supplement tests on compounds sent to UM for SDS, and compounds sent to MCV for SDS will have the TF, PPQ and TFA assays run on them. Occasionally. UM and MCV will continue with a precipitated withdrawal test in the rhesus monkey on compounds which obviously warrant it.

FURTHER TESTING

At this stage, for the last few years, recommendations would be made by an MCV/NIDA/NIH group as to whether the compound should receive further testing at MCV. In the future. recommendations for, or against, further work will also be made at the joint conference of MCV/UM/NIDA/NIH. Individually initiated research will continue as it has before and will be reviewed at the joint conference. Further work could, theoretically, consist of a primary addiction study in the monkey, rat infusion data. self-administration tests, or drug-discrimination procedures in monkey and/or pigeon. The data obtained by these procedures can be observed in the Annual Report to the Committee from MCV and UM. There is, both at MCV and UM, simultaneous with the attempt to obtain sufficient biological and biochemical data to ascertain whether we have an analgesic with or without dependence liability and characteristics which might tend to lead to abuse by man, an attempt to learn about some of the other fundamental actions of the drug. The results from this work on selected compounds are the subject of reports by both groups to the Committee at its scientific session. I might note that the drug discrimination procedure of UM is rather new and we hope to utilize it in the future as an additional method for determining the likelihood of abuse, by classification with subsets of compounds with documented abuse potential in man. Dr. J. Woods has reported on the procedure at Committee meetings.

SUPPORT

The Committee, to some extent, financially supports the work of UM and MCV and also supports the-joint meetings which are held. However, the bulk of the funds for these programs come from a NIDA grant and contract. The World Health Organization (WHO) also contributes to the drug testing program, through the Committee. Although it is a rather circuitous method, the Federal Government has supported, and continues to support, the work of the Committee to a much greater extent than pharmaceutical industry. Over two-thirds of the funds necessary for the work of the Committee come from NIDA and NIH. The money, of course, does not come directly to the Committee but to its testing units. Reports go to the Committee, the Government, and to the submitter of the drug.

NUMBER OF TESTS PERFORMED AT MCV/UM

We are, once again, very much indebted to the researchers in the Department of Pharmacology of the Medical College of Virginia and

the University of Michigan for the work which I shall be discussing. Among these are Drs. L. S. Harris, M. D. Aceto, W. L. Dewey and E. L. May from MCV, and Drs. H. H. Swain, J. H. Woods, A. Young, C. B. Smith and F. Medzihradsky from UM. The program at UM suffered from the untimely death of Mr. C. L. Fly. who ran part of the dependence testing program. An additional researcher, Dr. John Katz, will soon join their program.

This report concerns compounds which I received between May 1, 1979, and April 30, 1980, a rather arbitrary period for what I will denote as the "evaluation year." Of the ca. 118 compounds which I received at NIH for various tests, 25 new compounds were submitted to MCV and 23 new compounds to UM for evaluation in the single dose suppression test in the rhesus monkey. About 15 older compounds were evaluated in other tests (precipitated withdrawal, rat infusion, primary addiction, self-administration, etc.) at MCV and 8 older compounds were further evaluated at UM. Biochemical studies (binding affinity to rat brain homogenates, electrically stimulated guinea pig ileum and vas deferens preparations) on another set of 12 or so compounds submitted for these studies alone, were carried out at UM. Several compounds were sent to MCV for rodent antinociceptive tests., and the TFA assay, which did not receive further evaluation. Thus, about 80 compounds, altogether, were examined during this "evaluation year. " If one counts the number of "tests" run, where SDS. NW, PAS, self-administration, rat infusion, biochemical tests and antinociceptive tests are counted individually, about 90 such tests were carried out at MCV and ca. 70 tests at UM. One compound can, obviously, have multiple tests run on it and, thus, the number of reports submitted by MCV and UM are less than the number of tests. However, to compare the results of our testing units from year to year, we can look at the number of tests completed at each unit/year. Last year, UM completed ca. 73 tests, and MCV ca. 66. The observed annual fluctuation is directly related to the release, or non-release, of data from older compounds. This year, for example, we have an additional ca. 20 reports completed, but have not obtained consent from their submitter for release. Most of these will, hopefully, be included in next year’s reports. My previous estimate of the number of new compounds which would be received appears reasonable, and there is a regular flow of compounds.

ORIGIN OF SAMPLES -

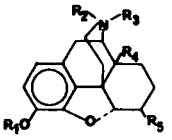
We have seen an increased interest in analgesics by several companies. Of the ca. 50 compounds which were new to the program this year, about 62 percent came from pharmaceutical industry (28 percent foreign, and 34 percent domestic), 36 percent came from U.S. universities, and 2 percent (one compound) came, more-or-less directly, from the WHO. This is the inverse of last year's figures of 40 percent from industry and 60 percent from universities, perhaps reflecting the increased difficulty university researchers are having at obtaining grants to synthesize analgesics, and a resurgence of interest in analgesics

by pharmaceutical companies. Although I have a feeling that these conclusions are valid, there is sufficient annual variation to allow the conclusion that submissions are evenly divided between University and Industry, the observed deviation from 50 percent being fortuitous.

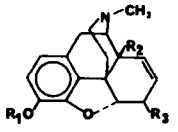
STRUCTURE-ACTIVITY RELATIONSHIPS OF COMPOUNDS IN THE MCV/UM REPORTS

The compounds in the MCV/UM reports can be classified as "morphine-like" (table 1), "methadone-like" (table 2), "morphinan-like" (table 3), "benzomorphan-like" (table 4), "pethidine-like" (table 5), and miscellaneous structures (tables 6-9). These 9 tables contain ca. 50 compounds. I eliminated compounds which presently appear to be of less interest, and those which have been adequately discussed heretofore. The tables contain excerpted data from the UM/MCV reports and thus could be called a "readers digest" of the CPDD. The complete data on each of the compounds can be found in the reports submitted by MCV and UM.

TABLE 1
"MORPHINE-LIKE" STRUCTURES



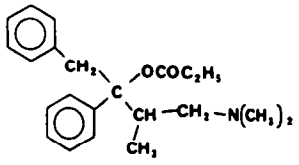
MIN #	R1	R2	R3	R4	R5	ED50 HP[a]	ED50 PPQ[b]	ACTIVITY IN MONKEY
9735	H	-	CPM[c]	H	=O	I[d]	0.009	ANTAGONIST
9629	H	CH3	ALLYL	OH	=O	I	-	ANTAGONIST (IMPURE?)
9630	H	CH3	CPM	OH	=O	I	-	NO EFFECT



MIN #	R1	R2	R3	BIOCHEMISTRY[e]
9701	H	SH	OH	AGONIST-LESS POTENT THAN MORPHINE
9702	CH3	SH	OH	AGONIST-LOW POTENCY
9703	CH3	NHCOCH3	OCOCH3	NEITHER AGONIST NOR ANTAGONIST-ENHANCES TWITCH
9704	CH3	NHCOCH2Cl	OCOCH3	ATYPICAL-ENHANCES TWITCH
9705	H	NHCOCH3	OCOCH3	ENHANCES TWITCH-HIGH PDC Ms RATIO[f]
9706	CH3	NH2	OCOCH3	AGONIST-LOW POTENCY, ATYPICAL
9707	CH3	Cl	=O	TRANSIENT INCREASE IN TWITCH
9708	H	Cl	=O	"MU" AGONIST
9709	H	Br	=O	AGONIST

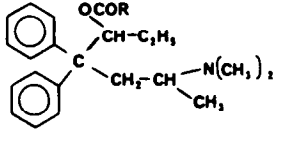
a) Hot plate assay (morphine = 1, codeine = 7). b)Phenylquinone writhing (morphine = 0.2, cyclazocine = 0.01). c) Cyclopropylmethyl. d) Inactive. e) Summary of rat brain homogenate, guinea pig ileum and vas deferens experiments. f) Additional work will be done.

TABLE 2
"METHADONE-LIKE" STRUCTURES"



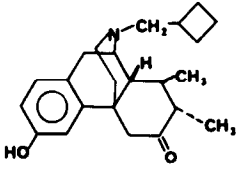
(+)-PROPOXYPHENE

NIH #	ED50 HP	ED50 PPQ	ED50 TFA	ACTIVITY IN MONKEY/BIOCHEMISTRY
9757	3.8	2.2	-	HIGH PDC. BIOCHEMICALLY RESEMBLED PETHIDINE, BUT HAD SOME NON-MORPHINE LIKE ACTIONS.

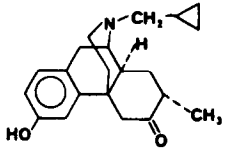


NIH #	R	ED50 HP	ED50 PPQ	ED50 TFA	ACTIVITY IN MONKEY
9004	CHC12	I	I	4.6	DID NOT SUBSTITUTE (TO 6gm/kg)
9048	CH2C6H5	4.5	1.8	-	DID NOT SUBSTITUTE (TO 8mg/kg)

TABLE 3
"MORPHINAN-LIKE" STRUCTURES

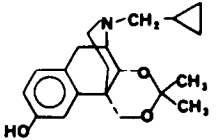


NIH #	ED50 HP	ED50 PPQ	ACTIVITY IN MONKEY/BIOCHEMISTRY
9622	4.5	0.4	HIGH PDC. MORE POTENT, LONGER ACTING THAN MORPHINE.



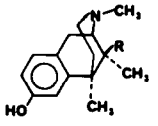
B/C TRANS

9623	13.7	0.7	ANTAGONIST

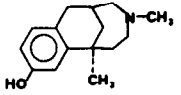


9538	0.2	0.04	HIGH PDC. PARTIAL SUBSTITUTION. NO PRECIPITATED WITHDRAWAL. PARTIAL SUBSTITUTION IN RODENT INFUSION. NOT CODEINE-LIKE IN SELF-ADMINISTRATION. BIOCHEMISTRY - DIFFERENT MECHANISM OF ACTION THAN MORPHINE; EXC COMPONENT.

TABLE 4
"BENZOMORPHAN-LIKE" STRUCTURES



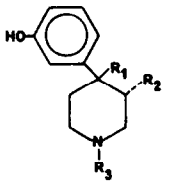
NIH #	R	ED50 HP	ED50 PPQ	ACTIVITY IN MONKEY/BIOCHEMISTRY
9628	(-)-CH2CH2CO(CH2)4CH3	2.4	0.2	ANTAGONIST. NON-SIGNIFICANT AMOUNT OF MORPHINE-TYPE DEPENDENCE IN PAS. NOT SELF-ADMINISTERED.
9625	(CH2)2CO(CH2)2CH(CH3)2	1.1	0.002	DOES NOT SUBSTITUTE FOR MORPHINE
9751	(+)-(CH2)2CO(CH2)2C5H9	D-R[a]	I	DOES NOT SUBSTITUTE FOR MORPHINE. MAY EXACERBATE WITHDRAWAL.
9752	(-)-9751	-[b]	-	LONG ACTING ANTAGONIST. NOT REVERSED BY MORPHINE. BIOCHEMISTRY - LIKE NALTREXONE, BUT INSURMOUNTABLE BY MORPHINE.



9612 dl	0.4	0.5	WEAK ANTAGONIST, STRONG DEPRESSANT PAS - NO SIGNIFICANT DEGREE OF DEPENDENCE
9613 (+)	2.6	0.9	ANTAGONIST
9614 (-)	1.8	0.5	WEAK ANTAGONIST OR STRONG DEPRESSANT[c]

a) No dose-response; 6 out of 10 mice were effected at 20mg/kg. b) No dose-response; 6 out of 10 mice were effected at 50mg/kg. c) Further work is in progress.

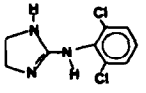
TABLE 5
"PETHIDINE-LIKE" STRUCTURES



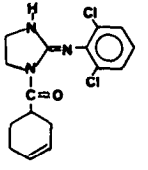
NIH #	R1	R2	R3	ED50 HP	ED50 PPQ	ACTIVITY IN MONKEY/BIOCHEMISTRY
9585	COC2H5	H	CH2C6H11	I[a]	-	NO EFFECT
9648	COC2H5	H	CH2CH2CH=CH2	0.3	-	HIGH PDC
9740	COC2H5	H	CH2CH2OCH3	0.7	0.9	HIGH PDC
9741	COC2H5	H	CH(CH3)(CH2)3CH3	I	-	NO EFFECT
9769	COC2H5	H	(CH2)5OCOCH3	24.	-	NOT MORPHINE-LIKE. ANTAGONISTIC PROPERTIES
9770	COC2H5	H	CH2CH2OCH2CH3	1.8	-	HIGH PDC
9772	COC2H5	H	CH2(CH2)4OH	I	-	NO EFFECT. BIOCHEMICALLY MORPHINE-LIKE
9771	CH(OH)C2H5	H	CH3	I	I	NO EFFECT
9729	CH(OCOCH3)C2H5 R-(p-ACETOXYPHENYL)	H	(CH2)4CH3	0.5	0.3	NO EFFECT.[b] BIOCHEMICALLY MORPHINE-LIKE IMPURE?
9783A	CH2CH2CH3	CH3	CH3	5.3	0.9	DOES NOT SUBSTITUTE. PAS - MILD TO MODERATE ABSTINENCE, NOT MORPHINE-LIKE.

a) Inactive. b) Additional work is in progress.

TABLE 6
MISCELLANEOUS STRUCTURES - A) "CLONIDINE-LIKE"

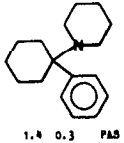


NIH #	ED50 HP	ED50 PPQ	ACTIVITY IN MONKEY
9571 - CLONIDINE	1.0	0.005	PARTIALLY SUBSTITUTES[a]



9460	13.	0.04	DOES NOT SUBSTITUTE.[b] PAS - VERY LOW DEPENDENCE

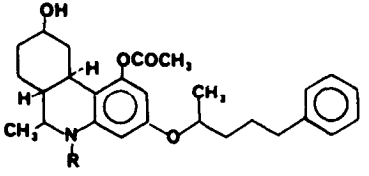
B) PHENCYCLIDINE



9580 - PCP	1.4	0.3	PAS - DEFINITE DEPENDENCE NALOXONE DOES NOT PRECIPITATE WITHDRAWAL.

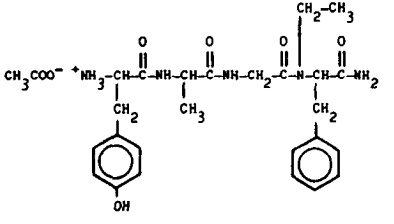
a) Rat Infusion - signs of withdrawal; lethal with morphine. Self-administration - does not maintain; non-morphine like sedative; strong behavioral effects. Biochemistry - Homogenate - no effect; ileum - potent agonist, not blocked by naloxone; vas deferens - agonist, blocked by naloxone. b) Poorly soluble; may not be absorbed.

TABLE 7
MISCELLANEOUS STRUCTURES - A) PHENANTHRIDINE - "THC-LIKE"



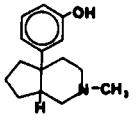
NIH #	R	ED50 HP	ED50 PPQ	ACTIVITY IN MONKEY/BIOCHEMISTRY
9513 dl	H	0.3	-	ATYPICAL CNS DEPRESSION, DYSPHORIA, CATATONIA, CONFUSION. *SELF-ADMINISTRATION - FAILED TO MAINTAIN.*
9596 (-)	H	0.15	0.1	PARTIALLY SUBSTITUTES. SELF-ADMINISTRATION - FAILED TO MAINTAIN.
9597 (-)	CH_3	0.02	0.06	SUBSTITUTES PARTIALLY

B) PEPTIDE



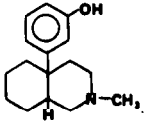
9725	0.7	0.06	HIGH PDC SELF-ADMINISTRATION - MAINTAINS AT 50% CODEINE RATE. BIOCHEMICAL - MORPHINE-LIKE, MORE POTENT *IN VITRO THAN IN VIVO.*

TABLE 8
MISCELLANEOUS STRUCTURES - A) PYRINDINYL



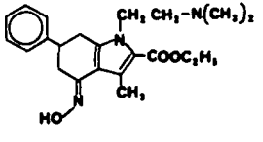
NIH #		ED50 HP	ED50 PPO	ACTIVITY IN MONKEY
9575	(+)-CIS	0.5	0.1	SUBSTITUTES PARTIALLY. DOES NOT PRECIPITATE TYPICAL WITHDRAWAL.
9576	(-)-CIS	2.4	0.6	SUBSTITUTES PARTIALLY. WEAK ANTAGONIST.

B) DECAHYDROISOQUINOLINE



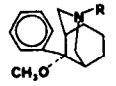
9577	(+)-CIS	0.9	0.2	SUBSTITUTES PARTIALLY AND BRIEFLY. DOES NOT PRECIPITATE WITHDRAWAL.
9578	(-)-CIS	2.9	0.6	HIGH PDC

C) PHENYLINDOLE OXIME



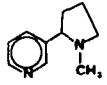
9550	5.5 - ORAL - 5.4		HIGH PDC

TABLE 9
MISCELLANEOUS STRUCTURES - A) AZABICYCLO(3.3.1)NONANES



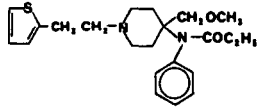
NIH #	R	ED50 HP	ED50 PPO	ACTIVITY IN MONKEY/BIOCHEMISTRY
9653	CH2CH=CH2	3.6	1.4	DOES NOT SUBSTITUTE
9654	(CH2)4CH3	2.6	0.2	HIGH PDC
9655	CH3	1.7	0.3	DOES NOT SUBSTITUTE
9673	CH2CH2C6H5	0.6	-	HIGH PDC

B) (-)-NICOTINE



9733	2.2	1.3	DOES NOT SUBSTITUTE. NOT A SPECIFIC ANTAGONIST. BIOCHEMICAL - LITTLE OR NO EFFECT.

C) SUFENTANIL



9726	0.004	0.0004	HIGH PDC SELF-ADMINISTRATION - MAINTAINS LIKE CODEINE. IT DIFFERS FROM MORPHINE, CONSIDERING

DISCUSSION

In table 1 a quaternary ammonium compound is listed (NIH 9629) which appears to have in vivo activity. We find this somewhat surprising since SC injected quaternary analgesic salts are not supposed to be able to traverse the blood brain barrier. A number of C-14 substituted compounds are listed with substituents other than the hydroxyl group, in table 1. No doubt, attempts will be made, in the future, to produce antagonists from some of them. Propoxyphene (table 2) was tested and found to have high physical dependence capacity (PDC). This is the dextro enantiomer. A methadone-like compound (NIH 9004) was found to have antagonist activity in the TFA assay. The SDS did not show it to be a particularly potent antagonist, if it is one in monkeys. Considerable tinkering has been done to the morphinan skeleton (table 3). Ring C was substituted with various substituents. NIH 9538 is particularly interesting in that it showed high PDC in the SDS test, but did not maintain codeine-like rates of self-administration. These tests might indicate that the compound would produce physical dependence, but not be abused by man. A comparable mono-oxygenated morphinan (NIH 9539) was reported last year. It was a potent agonist-antagonist and was not self-administered by monkeys. Peculiarly, NIH 9538 did not show antagonist activity in monkeys. It is one of the few, or the only, known N-cyclopropylmethyl substituted morphinan which does not have antagonist properties in the monkey.

Benzomorphans with an extended C-9 beta side-chain continue to be most interesting (table 4). Some are potent N-methyl agonist-antagonists. One pair of enantiomers (NIH 9751 and 9752) could conceivably serve as replacements for (+)- and (-)-naloxone, until NIDA completes its program of producing sufficient quantities of these enantiomers, based on the total synthesis of the opium alkaloids by Dr. Kenner C. Rice (NIH) which is scheduled to appear in the July issue of the Journal of Organic Chemistry. Unfortunately, these enantiomeric benzomorphans are not completely inert as agonists, although they do not show a dose-response relationship in the hot plate assay. The C-homobenzomorphans (NIH 9612 - 9614. in table 4) have been of interest and further work is continuing on one of them. Their hot plate ED50's have been confirmed and, evidently, the depressant action of the molecules caused the observed deviation from the expected relationship between racemate and enantiomers. The first 9 pethidine-like compounds noted in table 5 were part of a series in which it could be noted that as the agonist activity increased, so did PDC. However one compound (NIH 9729) appeared to be an exception to the generalization and it is being further evaluated. Experiments with clonidine (NIH 9571), a clonidine-like compound (NIH 9460) and PCP (NIH 9580) are summarized in table 6. Work on clonidine and PCP continued this year due to their interesting properties.

The peptide shown in table 7 is the first we have reported. It, like others reported in the literature, was a potent agonist with high PDC. We have not, as yet, seen a peptide with other than

high PDC. The pyrindinyl compounds in table 8 appear to be somewhat more interesting than the corresponding decahydroisoquinolines, as a series. The azabicyclo[3.3.1]nonanes in table 9 are. also, part of a series. Some of these may be quite interesting in the future. Further evaluation of some of the members of this series is contemplated if sufficient material can be obtained. The sufentanil, shown in table 9, was sent to the Committee at the instigation of WHO. It had high PDC, and is a very potent agonist. Work on the enantiomeric nicotines is continuing and will be the subject of a paper from MCV.

Once again we have seen compounds which resulted from modification of well-known structures and those which represent wide variations from known analgesics. Although it might have been assumed that we could guess, more or less correctly. at the dependence liability of variants of known structures, based on past structure-activity studies, in fact we would tend to be inaccurate a good bit of the time--sufficiently so as to warrant our continued examination of compounds whose structures, a priori. would not appear to be of much interest from a clinical viewpoint.

Thus, we note that medicinal chemists from universities and in industry are continuing their attempts to obtain useful analgesics. Some of the compounds which we have discussed may have good clinical potential, or are of theoretical interest, and are worthy of further study.

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Annual Report: Dependence Studies of New Compounds in the Rhesus Monkey (1980)

M. D. Aceto, L. S. Harris, W. L. Dewey, and E. L. May

All the test drugs were supplied by Dr. Arthur Jacobson, Medicinal Chemistry Section, NIAMDD, under the auspices of the Committee on Problems of Drug Dependence, Inc. Morphine was supplied by Dr. Robert Willette, National Institute on Drug Abuse. The chemical structures of the test compounds excluding yohimbine were unknown to us when they were submitted.

Three mouse tests were used in our 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 tests (TF vs M) and the phenylquinone test (PPQ) (Dewey et al. 1970; Dewey and Harris, 1971). Reference-standard data for these tests are shown in table 1. In addition, Dr. Jacobson supplemented these data and estimated starting doses which were 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 2.

This study was supported by a contract (#271-77-3404) from the National Institute on Drug Abuse, Dr. Heinz Sorer, Contract Officer. Technical assistance was provided by F. Tom Grove, R.F. Jones, and S.M. Tucker, Medical College of Virginia, Department of Pharmacology.

A rat continuous-infusion method was reported by Teiger (1974) and modified by Dewey and Patrick. Using this method, we can determine whether or not a drug will substitute for morphine in morphine-dependent rats or whether or not the drug per se will produce physical dependence.

Table 1
Comparative Data-ED_{50} Mg/Kg/Sc (95% C.L.) of Selected Standards in 3 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(0.12-.78)	0.011(0.0046-03)
Nalorphine .HCL	None at 10.0	2.6(0.69-9.75)	0.6(0.25-1.44)
Naloxone .HCL	None at 10.0	0.031(.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.

For the most part, the procedures described by Seevers and his colleagues (1936, 1963) and Deneau (1956) regarding the facilities and training of the monkeys were used and a brief description follows. The monkeys were injected with 3 mg/kg/sc of morphine sulfate every 6 hours for at least 90 days before being used. This dose schedule was reported by Seevers and Deneau (1963) to produce maximal physical dependence. Modified procedures for the precipitated withdrawal test (PPt-Withdrawal) and single dose suppression test (SDS) were reported by Aceto and coworkers (1974, 1977 and 1978). The PPt-Withdrawal test was initiated by the injection of a test drug 2 1/2 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 test compound was injected and the animals were observed for the suppression of abstinence 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 in a volume of 1 ml/kg 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 test. the animals of a group received the drug every 6 hours for 30-50 days. They were placed in abrupt withdrawal and challenged with naloxone periodically, and were observed for signs of physical dependence.

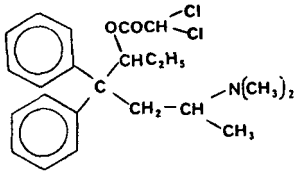
Table 2
Comparative Data (ED_{50} Mg/Kg) (95% S.E.) from the Hot Plate and Nilsen Test

Compound	Hot Plate Test	Nilsen Test
	Subcutaneous / Oral	Subcutaneous / Oral
Morphine Sulfate	0.98(0.83-1.1) / 6.3(4.7-8.3)	1.3(1.0-1.7) / 8.3(6.0-11.4)
Codeine Phosphate	6.8(4.5-10.2) / 13.5(9.7-18.7)	7.4(4.9-11.0) / 14.7(9.2-23.3)
Levorphanol Tartrate	0.2(0.1-0.3) / -	0.2(0.16-0.3) / 2.5(1.7-3.7)
Meperidine .HCL	5.3(4.0-7.1) / -	- / -
(-)-Metazocine.HBr	0.6(0.5-0.9) / 10.6(8.0-14.1)	0.5(0.3-0.7) / 26.0(21.0-33.0)
Dihydromorphinone .HCL	0.19(0.15-0.25) / 0.9(0.7-1.2)	0.2(0.15-0.3) / 1.8(1.5-2.1)
Nalorphine .HCL	9.9(5.7-17.1) / -	23.0(16.2-32.7) / -
Cyclazocine	1.5(1.1-2.1) / -	0.1(0.07-0.16) / -
Pentazocine	9.3(6.7-12.8) / -	6.5(4.4-8.8) / -
Chlorpromazine .HCL	1.1(0.9-1.5) / -	-
Naloxone .HCL and Naltrexone HCL	No Dose Response	

Phenobarbital, Amobarbital, Valium, Oxazepam, Flurazepam, Meprobamate and Mescaline are inactive on the hot plate test.

The Self-administration studies on rhesus monkeys are presented in a separate report in this monograph (Woolverton, et al,).

MCV 4030-NIH 9004. alpha-6-Dimethylamino-4,4-diphenyl-3-(2,2-dichloroacetoxy)heptane hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-5% at 1.0, 7% at 3.0 and 3% at 10.0

2) TF vs M-4.6 (1.64-12.88)

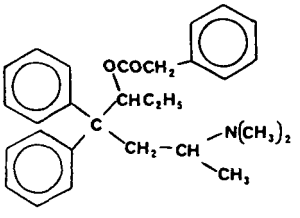
3) PPQ-2% at 10.0

4) HP-Inactive to 100.0

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	2 6.0	4 2.0	4 1.0	4 0.5	Vehicle-H_2O

This compound did not substitute for morphine in the dose range tested.

MCV 4041-NIH 9048-UM 1144. alpha-4,4-Diphenyl-6-dimethyl-amino-3-heptanol phenylacetate



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-7% at 1.0, 19% at 3.0 and 17% at 10.0

2) TF vs M-0% at 1.0, 4% at 3.0 and 8% at 10.0

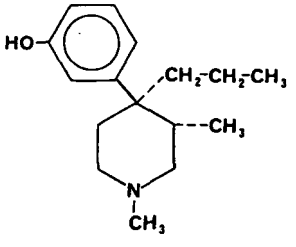
3) PPQ-1.76 (0.98-3.13)

4) HP-4.5 (3.2-6.4)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	2 16.0	2 8.0	2 4.0	Vehicle-H_2O + lactic acid

This compound did not substitute for morphine in the dose range tested.

MCV 4103-NIH 9343A-UM 1125A. m-(1,3-Dimethyl-4-propyl-4-piperidyl)phenol hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at doses up to 30.0

2) TF vs M-11.2 (4.9-26.3)

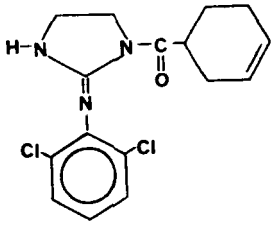
3) PPQ-0.9 (0.1-5.9)

4) HP-5.3 (3.2-8.5)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	4, 5.0	4, 2.5	4, 1.25	Vehicle-H_2O

MCV 4103 did not substitute for morphine in the dose range tested. The drug may have exacerbated withdrawal.

MCV 4126-NIH 9460. 1-(Cyclohex-3-enoic)-2-(2,6-dichlorophenyl amino)-2-imidazoline



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-22.2 (5.6-87.7)

2) TF vs M-Inactive at 3.0, 10.0 and 30.0

3) PPQ-0.04 (0.02-0.10)

4) HP-13.0 (10.0-16.9)

MONKEY DATA	#ANIMALS	4,	4,	4,	Vehicle-dil.
A. (SDS)	Doses (mg/kg/sc)	16.0	8.0	4.0	HCL + H_2O

In the dose range tested, MCV 4126 did not substitute for morphine, In three of four monkeys receiving the highest and lowest dose and in two of four monkeys receiving the intermediate dose, ataxia was noted. Some monkeys receiving drug were noted to be depressed and moving very slowly a day later.

B. (PPD)

Five non-dependent monkeys were given MCV 4126 suspended in ½% carboxymethylcellulose aqueous solution every 6 hours and observed for signs as designated below:

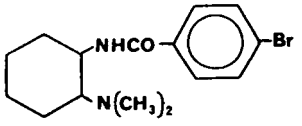
Day	Dose mg/kg/sc	Comments
1-7	2.0-4.0	The most common sign noted after drug was
8-15	6.0-14.0	drowsiness. Fighting and restlessness were
16 Abrupt Withdrawal and PPt-withdrawal		noted infrequently. During the first abrupt with-
12-24	18.0-38.0	drawal session (day 16), drowsiness, restlessness,
25-29	42.0-56.0	and wet dogs were noted 13-15 hours after the
30 Abrupt and PPt-withdrawal		drug was discontinued.

A naloxone challenge (0.5 mg/kg/sc) was given and a few additional signs were seen. During the 30-day, abrupt-withdrawal session drowsiness and wet dogs were seen and one monkey

vocalized when its abdomen was palpated. These animals were challenged with 5.0 mg/kg/sc of naloxone (n=4) and saline (n=1) the next day and only the signs designated as fighting, avoids contact, and wet dogs were seen.

Conclusion: Administered as a suspension, the morphine-like physical dependence liability of MCV 4126 appears to be very low.

MCV 4132-NIH 9469. trans-N-(2-Dimethylaminocyclohexyl)-4-bromo-benzamide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-14.7 (5.8-32.3)

2) TF vs M-15% at 3.0; 22% at 10.0 and 17% at 30.0

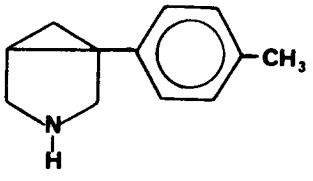
3) PPQ-3.3 (1.0-7.0)

4) HP-7.7 (5.7-10.4)

MONKEY DATA (PPt-Withdrawal)	#ANIMALS Doses (mg/kg/sc)	2, 6.0	3, 48.0	2, 24.0	1, 12.0

(Vehicle-1/2% carboxymethylcellulose, aqueous suspension). In the dose range tested, MCV 4132 did not precipitate withdrawal signs. Drowsiness was the principal sign observed.

MCV 4147-NIH 9542. 1-(4-Methylphenyl)-3-azabicyclo(3.1.0)hexane hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-30.9 (13.2-72.2)

2) TF vs M-Inactive at 10.0, 30.0 and 80.0

3) PPQ-4.8 (1.6-13.8)

4) HP-Non-determinable

MONKEY DATA A. (SDS)	#ANIMALS Doses (mg/kg/sc)	4, 24.0	4, 12.0	4, 6.0	Vehicle-H_2O

The drug substituted partially and very briefly for morphine

soon after it was injected. At the highest dose, the signs designated as lying on side or abdomen, restless, wet dog shakes and vomiting, vocalizes when abdomen palpated and rigid abdomen were suppressed. However, tremors and myoclonic spasms were much more prevalent, especially at the 2 higher doses. In addition, salivation was seen in 2 animals at the highest dose. Partial substitution does not necessarily imply that the drug has morphine-like dependence liability.

B. (PPD)

Five drug--naive monkeys were given MCV 4147 dissolved in water every 6 hours as indicated below:

Day	Doses mg/kg/sc	Comments
1-7	2.0-17.0	The effects noted with this drug included: Lying on side or abdomen, wet dogs, scratching, myoclonic jerks, yawning, drowsiness, fighting, salivation and vomiting. During Day 18 abrupt withdrawal, we saw restlessness in all animals, and myoclonic jerks between 14-17 hours after drug was withdrawn. No remarkable effects were seen after naloxone. On Day 23, one monkey was found dead.
8-14	19.0-31.0	
15-17	33.0-35.0	
18 Abrupt & PPt-Withdrawal		
19-25	35.0-30.0	
26-32	36.0-36.0	
33-39	36.0-43.0	
40 Abrupt & PPt-Withdrawal		

During withdrawal on day 40 at 12-18 hours after the last injection, we noted fighting 2/4; restlessness 4/4; tremors 1/4; wet dogs 1/4; retching 1/4; scratching 2/4. No remarkable signs were seen during precipitated withdrawal with 2.0 mg/kg naloxone.

Conclusion: MCV 4147 does not produce morphine-like physical dependence. Relatively little tolerance was seen to develop to this drug. All the animals bled from the site of injection just after each injection beginning on day 8 to the end of the study. One animal died during the study. Body weights remained about the same throughout the experiment.

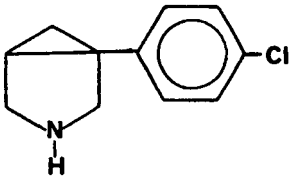
MCV 4148-NIH 9543. 1-(4-Chlorophenyl)-3-azabicyclo(3.1.0)hexane hydrochloride

MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 10.0 and 100.0

339-844 0 - 81 - 21

MCV 4148-NIH 9543 (continued)



2) TF vs M-Inactive at 10.0 and 100.0

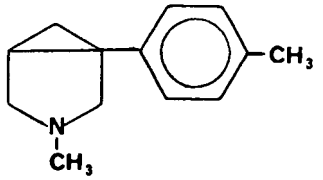
3) PPQ-16.4 (8.1-33.1)

4) HP-No dose response

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	3, 24.0	3, 12.0	3, 6.0	Vehicle-H_2O

This compound did not substitute for morphine at any of the doses tested. Myoclonic jerks were noted in 2 of the animals receiving the intermediate dose.

MCV 4150-NIH 9544. 3-Methyl-1-(4-methylphenyl)-3-azabicyclo(3.1.0) hexane hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 10.0 and 30.0

2) TF vs M-Inactive at 10.0 and 30.0

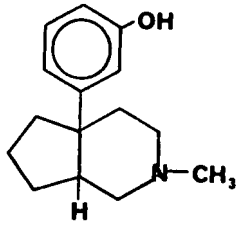
3) PPQ-4.3 (1.3-14.5)

4) HP-19.1 (13.5-27.0)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	3, 24.0	3, 12.0	3, 6.0	Vehicle-H_2O

MCV 4150 did not substitute for morphine. The drug appeared to exacerbate withdrawal. Salivation was noted at 2 higher doses.

MCV 4156-NIH 9575. cis-(+)-3-(Octahydro-2-methyl-1H-2-pyrindin 4a-yl)phenol, (Z)-2-butenedioic acid salt



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-2.2 (0.7-7.2)

2) TF vs M-Inactive at 1.0, 3.0 and 10.0

3) PPQ-0.13 (0-05-0.4)

4) HP-0.46 (0.33-0.64)

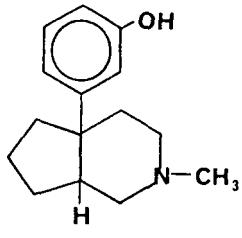
MONKEY DATA	#ANIMALS	3 ,	3 ,	3 ,	Vehicle-H_2O
A. (SDS)	Doses (mg/kg/sc)	2.0	1.0	0.5	

The drug substituted partially for morphine. Partial substitution does not necessarily imply that the compound has morphine-like properties. Initially, some restlessness (pacing) was seen which was soon followed by drowsiness. A challenge dose of naloxone (0.1 mg/kg/sc) was given to the monkeys of another group receiving this drug or morphine and the animals promptly went into withdrawal.

MONKEY DATA	2 ,	3 ,	3 ,	1 ,	Vehicle-H_2O
B. (PPt-Withdrawal)	8.0	4.0	2.0	1.0	

MCV 4156 elicited the symptoms designated: drowsiness, restlessness, wet dogs salivation and jaw sag. However, the animals did not vocalize when their abdomens were palpated nor was retching or vomiting observed after MCV 4156. The drug does not precipatate a typical withdrawal reaction in the dose range tested.

MCV 4157-NIH 9576-UM 1242. cis-(-)-3-(Octahydro-2-methyl-1H-2-pyrindin-4a-yl)phenol, (Z)-2-butenedioic acid salt



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-10.4 (3.3-33.2)

2) TF vs M-60.5 (12.8-286.8)

3) PPQ-0.6 (0.3-1.9)

4) HP-2.4 (1.6-3.7)

MONKEY DATA	#ANIMALS	3 ,	3 ,	2 ,	Vehicle-H_2O
A. (SDS)	Doses (mg/kg/sc)	32.0	16.0	8.0	

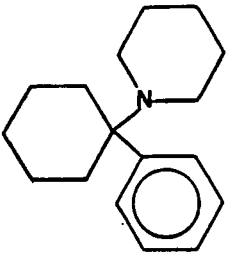
This drug substituted partially for morphine. Drowsiness was noted at all doses tested. Partial substitution does not necessarily imply that the compound has morphine-like properties.

MONKEY DATA	1 ,	3 ,	3 ,	2 ,	Vehicle-H_2O
B. (PPt-Withdrawal)	48.0	32.0	16.0	8.0	

At the highest dose, tremors, wet dogs, retching and convulsions were observed within the first 30 minutes after drug. The animal was given pentobarbital to terminate the convulsions. At the 32.0-mg dose, drowsiness, avoids contact, restlessness, tremors, wet dogs, retching, vomiting and salivation were seen. However, the animals did not vocalize when their abdomens were palpated. Drowsiness was the principal sign noted at the two lower doses.

The drug appears to elicit many withdrawal signs. It is considered to have weak antagonist properties.

MCV 4158-NIH 9580. 1-(1-Phenylcyclohexyl)piperidine hydrochloride (Phencyclidine)



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 1.0, 3.0 and 10.0

2) TF vs M-0.3 (0.1-1.0)

3). PPQ-1.4 (0.5-4.1)

4) HP-Not Tested

MONKEY DATA

Primary Physical Dependence

Five drug-naive animals were given MCV 4158 every 6 hours or as indicated below subcutaneously. The drug was dissolved in H_2O. The animals were observed for drug-behavioral effects approxlmately 1/2 hour after administration for 15 minutes. During abrupt or precipitated withdrawal, the animals were observed as indicated below:

Day	Dose mg/kg/sc 4 x day	Comments
1-3	0.1	Frequently noted signs were
4-5	0.2	slowing, ataxia, restlessness,
6	0.3	body sag, and staring. Some
7	0.4	were quite severe. Tolerance
8-9	0.5	developed to drowsiness.
10-13	0.4	Less frequently seen signs were: lying on side, fighting, avoids contact, lip-licking, and jaw sag.
14-15	0.5	
16-17	0.55	
18-19	0.6	
20-21	0.65	
22-23	0.7 6 x day	
24	0.45 6 x day	
25-26	0.7 6 x day	
27-28	0.45 6 x day	
29-30	0.5 6 x day	

Day 31 Abrupt withdrawal

Hours in Withdrawal	Comments
12¼	1/5 fighting, tremor, wet dogs, 2/5 avoids contact

Hours in Withdrawal	Comments
13¼	1/5 restless, 1/5 tremors, 2/5 fighting, 2/5 avoids contact
14¼	1/5 lying on side, tremors, retching, restless, yawning; 215 fighting
15	1/5 lying on side, fighting, crawling, tremors, yawning and avoids contact; 2/5 restless, wet dogs 3/5 myoclonic jerks; 5/5 Drowsy
18	1/5 fighting, avoids contact; 2/5 myoclonic jerks; 5/5 restless
24	1/5 avoids contact

Day	Dose	
32-34	0.7	
35-36	0.6	
37	Precipitated withdrawal	Little difference between the naloxone (0.5 mg/kg/sc) and saline-challenged animals.
38-40	0.6	
41-50	0.7	
51	Abrupt withdrawal	

Hours in Withdrawal	Comments
14	1/5 avoids contact, vocalizes, slowing, yawning, vocalizes when abdomen palpated; 2/5 fighting; 4/5 tremors; 5/5 restless
19	1/5 avoids contact, slowing, yawning, 2/5 fighting, tremors, vocalizes when abdomen palpated; 5/5 restless
24	1/5 avoids contact; 2/5 slowing, fighting, vocalizes when abdomen palpated; 5/5 restless
36	1/5 fighting, avoids contact, restless; 2/5 wet dogs
48	No Signs
72	1/5 fighting, avoids contact
102-120	No Signs

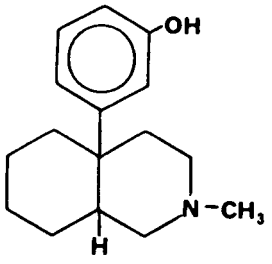
Conclusions: With the exception of drowsiness, MCV 4158 produces many side effects to which little tolerance develops. The drug has a rapid onset of action (15 to 30 minutes) and a short duration of action (1 to 2 hours).

The severity of withdrawal signs appears to increase when the drug is given more frequently and there is some resemblence of these signs to those seen when morphine is withdrawn in morphine-dependent monkeys. Naloxone did not precipitate withdrawal.

When the body weights taken at the beginning of the experiment are compared to those noted at the end, 2 animals lost weight (0.4 to 0.5 Kg), 2 gained weight (0.3 Kg) and one showed no difference.

This drug has a definite physical dependence liability and more studies are recommended.

MCV 4159-NIH 9577. cis-(+)-3-(Decahydro-2-methyl-4a-isoquinolinyl)phenol, (Z)-2-butenedioic acid salt



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-13.0 (4.3-39.3)

2) TF vs M-18.0 (7.9-40.5)

3) PPQ-0.23 (0.06-0.86)

4) HP-0.88 (0.66-1.2)

MONKEY DATA	#ANIMALS				
A. (SDS)	Doses (mg/kg/sc)	3, 4.0	3, 2.0	3, 1.0	Vehicle-H_2O

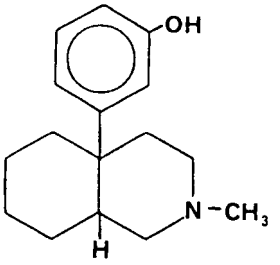
In the dose range tested, MCV 4159 substituted partially and briefly for morphine. Partial substitution does not necessarily imply that the compound has morphine-like properties.

MONKEY DATA	#ANIMALS					
B. (PPt-Withdrawal)	Doses (mg/kg/sc)	1, 32.0	2, 16.0	3, 8.0	2, 4.0	1, 2.0	Vehicle-H_2O

In the dose range studied, the drug did not precipitate withdrawal. Drowsiness was the only sign seen consistently.

MCV 4160-NIH 9578. cis-(-)-3-(Decahydro-2-methyl-4a-isoquinolinyl)phenol, (Z)-2-butenedioic acid salt

MCV 4160-NIH 9578 (continued)



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-62.6 (15.0-260.5)

2) TF vs M-40.0 (16.1-99.4)

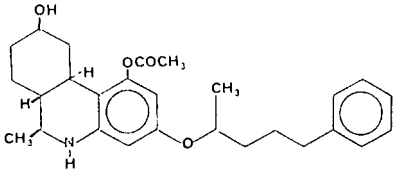
3) PPQ-0.6 (0.2-2.1)

4) HP-2.9 (1.9-4.3)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	3 32.0	3 16.0	3 8.0	Vehicle-H_2O

MCV 4160 substituted completely for morphine. At the highest dose, 3/3 showed tremors, 2/3 were restless and 1/3 salivated.

MCV 4161-NIH 9596. (-)-trans-5,6,6a-beta,7,8,9,10,10a-alpha-Octahydro-1-acetoxy-9-beta-hydroxy-6-beta-methyl-3-(5-phenyl-2-pentyloxy)-phenanthridine hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-1.7 (0.6-5.0)

2) TF vs M-Inactive at 3.0, 10.0, and 30.0

3) PPQ-0.1 (0.04-0.3)

4) HP-0.15 (0.13-0.19)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	3 0.5	3 0.25	3 0.125	Vehicle-Propylene Glycol + H_2O

This compound substituted partially for morphine at all doses tested. The signs drowsiness, eyelids ptosis were noted in most of the animals and slowing was seen in one monkey at each dose.

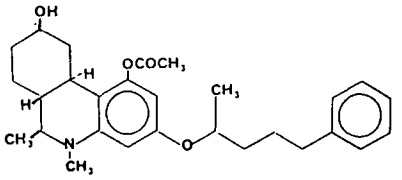
Partial substitution does not necessarily imply that the compound has morphine-like properties.

MCV 4162-NIH 9597. (-)-trans-5,6,6a-beta,7,8,9,10,10a-alpha-Octahydro-1-acetoxy-9-beta-hydroxy-5,6-beta-dimethyl-3-(5-phenyl-2-pentyloxy-phenanthridine hydrochloride

MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-0.1 (0.04-0.3)

MCV 4162-NIH 9597. (continued)



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

2) TF vs M-Inactive at 0.03, 0.1, 0.3, and 30.0

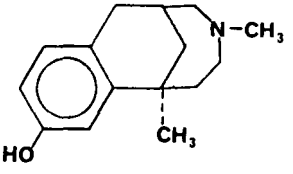
3) PPQ-0.06 (0.02-0.2)

4) HP-0.016 (0.011-0.023)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	1 0.16	1 0.08	3 0.04	3 0.02	3 0.01	1 0.005	Vehicle-Propylene Glycol + H_2O

At the two higher doses, MCV 4162 substituted partially for morphine. However, tremors were noted at these doses. In addition, at the highest dose, ataxia was seen. Drowsiness was seen at all doses tested. Partial substitution does not necessarily mean that the drug has morphine-like properties.

MCV 4167-NIH 9612. dl-9-Hydroxy-4,7-dimethyl-C-homobenzomorphan hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-1. 6.4 (3.9-10.5)
2. 15.5 (7.4-32.2)

2) TF vs M-1. 19.8 (10.5-37.2)
2. 24.9 (10.8-57.4)

3) PPQ-0.5 (0.2-1.3)

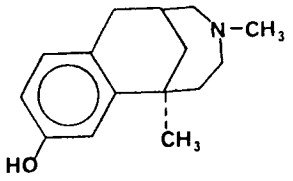
4) HP-1. 0.4 (0.25-0.6)
2. 0.49 (0.36-0.65)

MONKEY DATA (PPt-Withdrawal)	#ANIMALS Doses (mg/kg/sc)	3 18.0	3 9.0	3 4.5	Vehicle-carboxymethyl cellulose suspension

The principal signs noted at the highest dose were drowsiness, lying on side or abdomen, ataxia, and for 30-45 minutes, the animals were unable to move about and appeared to be anesthetized. One animals vocalized when its abdomen was palpated, 2 retched and 1 was restless. At the lowest dose, drowsiness was the principal sign seen, 1 was fighting, 1 was restless, 1 showed tremors, and 1 salivated.

This drug appears to have very weak antogonist and very strong depressant properties.

MCV 4168-NIH 9613. (+)-9-hydroxy-4.7-dimethyl-C-homobenzomorphan hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

1) TF-1. 8.2 (3.1-21.8)
2. 6.7 (2.5-18.4)

2) TF vs M-1. Inactive at 3.0, 6.0, 10.0, and 30.0
2. Inactive at 3.0, 3.0, 10.0, and 30.0

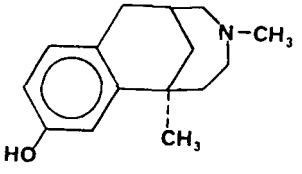
3) PPQ-1. 0.3 (0.1-1.0)
2. 0.9 (0.4-2.2)

4) HP-1. 2.6 (2.1-3.4)
2. 2.4 (1.4-4.0)

MONKEY DATA	#ANIMALS	3	3	3	Vehicle-H_2O
(PPt-Withdrawal)	Doses (mg/kg/sc)	10.0	5.0	2.5	

Dose-related precipitated withdrawal was seen. All the animals showed ataxia at the highest dose. At the 2 higher doses, it seemed to the observer that some of the animals were unable to vocalize when the abdomen was palpated.

MCV 4169-NIH 9614. (-)-9-Hydroxy-4.7-dimethyl-C-homobenzormorphan hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

1) TF-1. Inactive at 3.0, 6.0, 10.0, and 30.0
2. Inactive at 3.0, 10.0, and 30.0

2) TF vs M-1. 13.4 (5.7-31.3)
2. 5.5 (1.2-25.9)

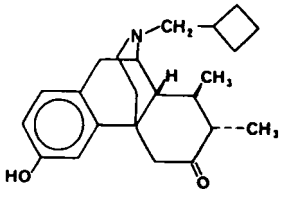
3) PPQ-1. 0.5 (0.2-1.7)
2. 0.4 (0.1-.1.3)

4) HP-l. 1.8 (1.3-2.4)
2. 2.5 (1.9-3.3)

MONKEY DATA (PPt-Withdrawal)	#ANIMALS Doses (mg/kg/sc)	3, 3, 3, 12.0 6.0 3.0 Vehicle-H_2O

Certain signs designated as lying on side or abdomen, drowsiness, ataxia, restlessness and tremors were seen. However, only one animal retched, one salivated, and two vocalized when the abdomen was palpated. This drug appeared to have very weak antagonist and/or strong depressant properties.

MCV 4171-NIH 9622. 3-Hydroxy-6-0x0-7-alpha,8-beta-dimethyl B/C-cis N-cyclobutyl-methylmorphinan



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, and 30.0

2) TF vs M-0.2 (0.1-0.8)

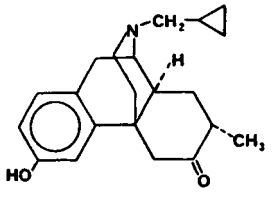
3) PPO-0.4 (0-1-1.9)

4) HP-4.5 (3.4-5.9)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	3, 3, 4, 1, 3.0 1.5 0.75 0.16 1, Vehicle-H_2O 0.04

MCV 4171 substituted completely for morphine in the dose range of 0.75-3.0. The drug has a prompt onset of action and a long duration of action. Two out of three monkeys receiving the highest dose did not require morphine for approximately 6 hours and all the monkeys receiving the 0.75 dose also did not require morphine for approximately 6 hours. The drug appears to be much more potent and longer acting than morphine.

MCV 4174-NIH 9623. 3-Hydroxy-6-oxo-7-alpha-methyl-B/C-trans-N-cyclopropylmethylmorphinan hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-17.3 (5.4-55.5)

2) TF vs M-0.6 (0.2-2.2)

3) PPO-0.7 (0.1-3.3)

4) HP-13.7 (9.6-19.5)

MCV 4174 (continued)

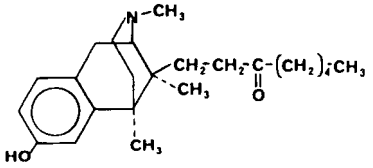
MONKEY DATA	#ANIMALS	2	2	2	
A. (SDS)	Doses (mg/kg/sc)	1.0	0.5	0.25'	Vehicle - 1/2% carboxymethylcellulose aqueous suspension.

Because of the severe exacerbation of withdrawal signs, all the animals were injected with morphine from 45 to 90 minutes after receiving MCV 4174. Thirty minutes later, some of the animals still vocalized during abdominal palpation and showed severe tremors. Salivation and jaw sagging were noted in some animals.

MONKEY DATA	#ANIMALS	3	3	3
B. (PPt-Withdrawal)	Doses (mg/kg/sc)	1.0	0.5	0.25
		Vehicle-H_2O		

The drug promptly precipitated dose-related withdrawal signs in all the monkeys. After 90 minutes all the animals were given morphine to alleviate severe withdrawal. At the highest dose, one monkey still vocalized during abdominal palpation; jaw sag and salivation were also observed in most animals at the highest dose.

MCV 4175-NIH 9624-UM 1258. 1-[(2-alpha, 6-alpha, 11S)-dl-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl]-3-octanone methanesulfonate.



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, and 30.0

2) TF vs M-0.03 (0.08-0.07)

3) PPQ+0.2 (0.08-0.6)

4) HP-2.4 (1.7-3.3)

MONKEY DATA
(Primary Physical Dependance)

A group of 5 monkeys which had not received any drug for at least 3 months was given MCV 4175 every 6 hours as indicated below and observed for behavioral signs for approximately 15 minutes, 1/2 hour after drug was administered. The drug was dissolved in H_2O. During abrupt or precipitated withdrawal the animals were observed as indicated below:

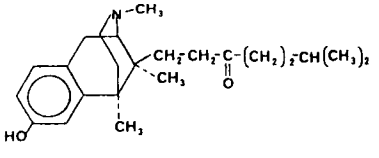
DAY	DOSE mg/kg/sc	COMMENTS
1	0.1	Drowsy

DAY	DOSE mg/kg/sc	COMMENTS
2	0.2	Drowsy
3-4	0.4	Drowsy
5	0.8	Drowsy
6	1.6	Drowsy
7	3.2	Drowsy, slowing, some sedation; jaw sag.
8-12	3.8	Lying on side, drowsy, slowing, some vomiting and coughing, salivation, and jaw sag. One animal convulsed. Sores began developing at sites of injections. Weight loss in all animals.
13-15	2.4	Dose was reduced but animals were drowsy and one was very depressed, some salivation also noted. Some animals convulsed on day 14.
16	ABRUPT WITHDRAWAL	One animal avoided contact, some restlessness, wet dogs. Animals less drowsy in withdrawal.
17	2.6	Drowsy, some salivation, tremors and avoids contact.
18	2.8	Drowsy, fighting, coughing and salivation.
19	3.2	Drowsy, some salivation, fighting, coughing and scratching.
20	3.6	Drowsy, scratching, some avoided contact, slowing, wet dogs, and salivation.
21	3.8	Drowsy, some fighting, wet dogs, retching, coughing, salivation, and scratching. One animal developed sores on back.
22-24	4.0	On day 22, drowsy, some lying on side, severe tremors, wet dogs, salivation and scratching. Three monkeys had sores on backs. On day 23, drowsy, some salivation, avoids contact, sagging and scratching. On day 24, drowsy, and scratching. One monkey found dead at midnight; dose reduced.

25	2.0	Drowsy, some lying on side, sagging, wet dogs.
26	2.4	Drowsy, some avoid contact, ataxia, restlessness, retching, coughing, salivation and scratching.
27	2.8	Drowsy, some fighting, salivation and scratching.
28-29	3.2	Drowsy and scratching, some jaw sag, and salivation. Sores on back.
30	ABRUPT WITHDRAWAL	Drowsy, scratching, and wet dog
30	PPt-WITHDRAWAL	Challenged with 2.0 mg/kg of maloxone Lying on side or abdomen, restless, scratching, wet dogs, retching, and coughing were seen.
		Another monkey died 11 days later.

CONCLUSION: MCV 4175 does not produce a significant degree of morphine-like dependence. Little tolerance developed to the effects of the drug. Drowsiness was the principal side effect seen. The drug does not appear to be well tolerated.

MCV 4176-NIH 9625. 1-[(2-alpha,6-alpha,11S)- dl-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl]-6-methyl-3-heptanone methanesulfonate



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, and 30.0

2) TF vs M-14.8 (3.7-58.6)

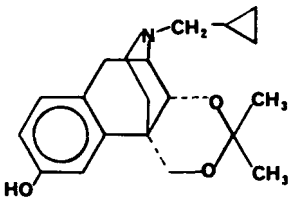
3) PPQ-0.002 (0.0003-0.01)

4) HP-1.1 (0.8-1.3)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)	20.0	10.0	5.0	Vehicle-H_2O

MCV 4176 did not substitute for morphine. At the highest dose, convulsions were noted in one animal 10 minutes after receiving drug. The convulsions were terminated with a pentobarbital injection. Severe tremors were also seen in one monkey receiving the 10.0 mg/kg dose. MCV 4176 was tested previously in the SDS test in the dose range 0-62-5.0 mg/kg/sc.

MCV 4177-NIH 9538-UM 1167. (-)-17-Cyclopropylmethyl-7,7-dimethyl-3-hydroxy-6,8-dioxamorphinan d-tartrate methanolate)



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, and 30.0

2) TF vs M-0.03 (0.01-0.08)

3) PPQ-0.04 (0.2-2.0)

4) HP-0.21 (0.18-0.26)

MONKEY DATA	#ANIMALS				
A. (SDS)	Doses (mg/kg/sc)	3	4	3	1
		0.5	0.25	0.125	0.016

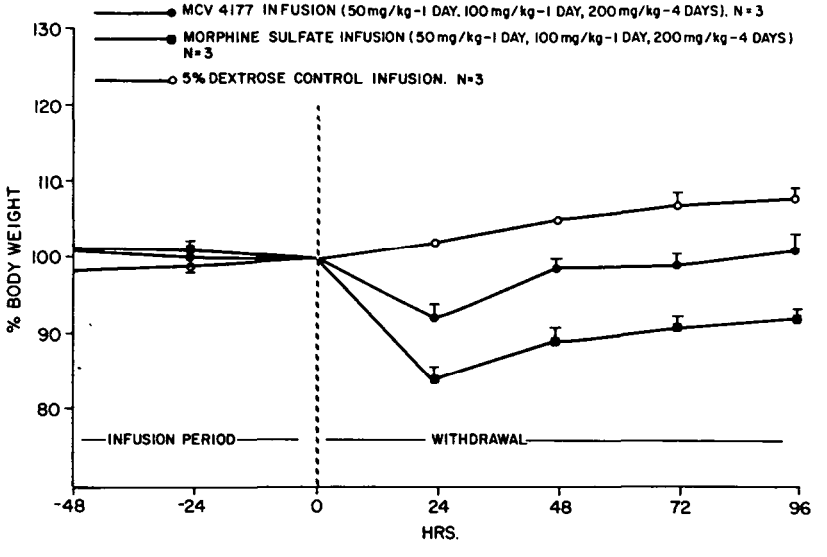
Vehicle-H_2O

More studies at lower doses will have to be done to state whether or not the compound sustitutes completely for morphine. At the higher doses, ataxia, slowing, jaw sag, ptosis and drowsiness were noted and partial substitution for morphine was seen. Partial substitution does not necessarily mean that the drug is morphine-like.

MONKEY DATA	#ANIMALS				
B. (PPt-Withdrawal)	Doses (mg/kg/sc)	2	2	2	Vehicle-H_2O
		1.0	0.25	0.06	

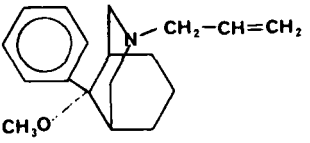
MCV 4177 did not precipitate withdrawal. The animals were drowsy and slow, were salivating and showed jaw and body sag at all doses. Some of the animals receiving drug did not require the noon injection of morphine and were given morphine 2 1/2 hours later.

EAT INFUSION (PPD)



When given in the same dose regimen as morphine, MCV 4177 produces substantial signs of physical withdrawal, but less than that of morphine, as shown by the weight-on data above. Fewer withdrawal signs were noted when compared to morphine.

MCV 4180-NIH 9653. 3-Allyl-9-beta-methoxy-9-phenyl-3-azabicyclo-[3.3.1]nonane hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-25.0 (11.2-55.8)

2) TF vs M-0% at 3.0, 10% at 10.0, and 34% at 30.0

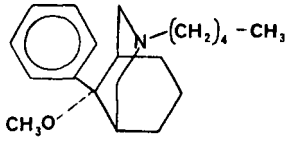
3) PPQ-1.4 (0.6-3.3)

4) HP-3.6 (2.6-5.0)

MONKEY DATA	#ANIMALS	1	, in one hour.
Preliminary (SDS)	Doses (mg/kg/sc)	22.0	

Up to a cumulative dose of 22.0 mg/kg, (2.0, 4.0, 8.0, and 8.0 mg/kg every 15 minutes), MCV 4180 did not substitute for morphine. Drug supply was exhausted.

MCV 4181-NIH 9654. 3-n-Amyl-9-beta-methoxy-9-phenyl-3-azabicyclo-{3.3.1} nonane hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-5.2 (2.1-32.2)

2) TF vs M-Inactive at 3.0, 10.0, and 30.0

3) PPQ-0.2 (0.1-0.7)

4) HP-2.6 (1.9-3.5)

MONKEY DATA	#ANIMALS	2	3	3	, Vehicle-H_2O
(SDS)	Doses (mg/kg/sc)	2.0	1.0	0.5	

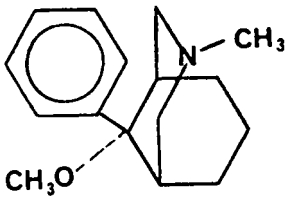
MCV 4181 substituted completely for morphine at the highest dose. The drug had a prompt onset of action. The duration of action was 2-3 hours.

MCV 4182-NIH 9655. 3-Methyl-9-beta-methoxy-9-phenyl-3-azabicyclo-[3.3.1]nonane citrate hemihydrate

MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-10.0 (3.2-31.0)

MCV 4182-NIH 9655 (continued)



MOUSE DATA-ED_{50} (95% C.L.)-

2) TF vs M-0% at 3.0, 21% at 10.0, and 29% at 30.0

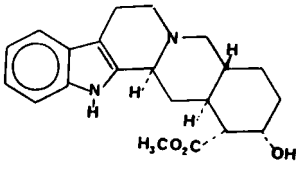
3) PPQ-0.3 (0.1-1.0)

4) HP-1.7 (1.3-2.2)

MONKEY DATA (SDS)	#ANIMALS Doses (mg/kg/sc)					
	1	2	1	2	2	
	32.0	24.0	16.0	12.0	6.0	Vehicle-H_2O + Lactic Acid

This drug did not substitute for morphine in the dose range tested.

MCV 4184-NIH 9689. Yohimbine hydrocholoride



MOUSE DATA-ED_{50} (95% C.L.)- (mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, and Text

2) TF vs M-5.6 (2.7-11.5)

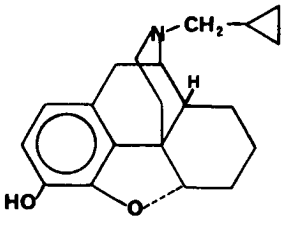
3) PPQ-17.1 (6.6-44.1)

4) HP-Not Tested

MONKEY DATA (PPt-Withdrawal)	# ANIMALS Doses (mg/kg/sc)					
	1	1	1	1	2	
	0.25	0.06	0.01	0.001	0.002	
	2	Vehicle-H_2O				
	0.0005					

MCV 4184 did not precipitate withdrawal in the dose range tested. The only signs noted, especially in the dose range 0.01-0.002, were salivation, avoids contact and jaw sag.

MCV 4185-NIH 8437, UM 774. N-Cyclopropylmethylnordesomorphine hydrochloride



MOUSE DATA-ED_{50} (95% C.L.)- (mg/kg/sc)

1) TF-Inactive at 3.0, 10.0, and 30.0

2) TF vs M-0.3 (0.1-1.1)

MCV 4185-NIH 8437, UM 774. (continued)

MOUSE DATA ED_{50} (95% C.L.)-
(mg/kg/sc)

3) PPQ-3.5 (1.7-7.4)

4) HP-4.5 (2.7-7.4)

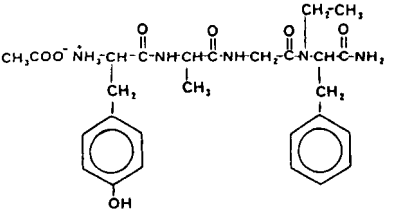
MONKEY DATA	#ANIMALS				
A. (SDS)	Doses (mg/kg/sc)	2, 0.1	2, 0.05	2, 0.025	Vehicle-H_2O

MCV 4185 did not substitute for morphine. Salivation was noted at the 2 higher doses. One monkey at the highest dose ejaculated 3 times during the first 1/2 hour.

MONKEY DATA	#ANIMALS					
B. (PPt Withdrawal)	Doses (mg/kg/sc)	2, 0.2	2, 0.1	3, 0.01	4, 0.05	
		3, 0.003	1, 0.008	Vehicle-H_2O		

This compound precipitated withdrawal in doses as low as 0.003 mg/kg. The drug acts promptly and has a longer duration of action than naloxone. MCV 4185 is approximately 10 times as potent as naloxone. Salivation was noted occassionallv and was not dose-related.

MCV 4188-NIH 9725, UM 1213. L-Tyrosyl-D-alanylglycyl-L-N-alpha-ethylphenylalanine amide acetate.



MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

1) TF-1.2 (0.3-5.3)

2) TF vs M-Inactive at 0.01, 0.03. 0.1, 1.0 and 30.0

3) PPQ-0.064 (0.018-0.22)

4) HP-0.73 (0.59-0.90)

MCV 4189-NIH 8735A, UM 909. 2-(2-Methyl-3-furymethyl)-2'-hydroxy-5,9-alpha-dimethyl-6,7-benzomorphan methanesulfonate.

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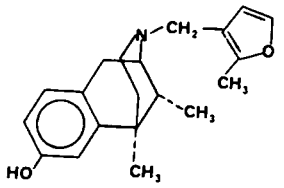
MCV 4189-NIH 8735A-UM 909.(continued)



MOUSE DATA ED_{50} (95% C.L.)-
(mg/kg/sc)

1) TF-5.1 (1.9-13.7)

2) TF vs M-Inactive at 1.0, and 10.0

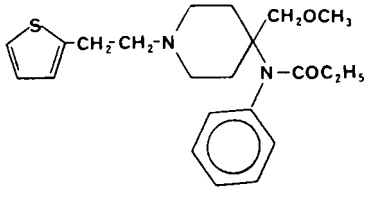
3) PPQ-0.72 (0.38-1.36)

4) HP-1.9 (1.5-2.5)

MONKEY DATA (SDS) #ANIMALS Doses (mg/kg/sc) 3, 3, 3, Vehicle-H_2O 8.0 4.0 2.0

This compound did not substitute for morphine although it sharply reduced the incidence of retching and lying on side. The signs designated ataxia and sagging were also noted at the highest dose.

MCV 4191-NIH 9726-UM 1214. N-[4-(Methoxymethyl)-1-(-2-(2-thienyl) ethyl)-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propane-tricarboxylate (1:1). (Sufentanil citrate)



MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

1) TF-0.011 (0.004-0.03)

2) TF vs M-Inactive at 30.0, 1.0, 0.03, 0.003 and 0.0003

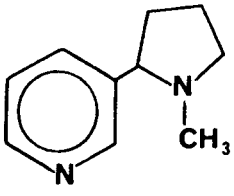
3) PPQ-0.0004 (0.0001-0.0015)

4) HP-0.004 (0.003-0.005)

MONKEY DATA (SDS) #ANIMALS Doses (mg/kg/sc) 3, 3, 3, Vehicle-H_2O 0.004 0.002 0.001

At the higher doses, MCV 4191 substituted completely for morphine. The drug acts promptly and is approximately 1000 x as potent as morphine. Its duration of action is at least as long as that of morphine. Some of the animals receiving the drug also appeared to be drowsy.

MCV 4194-NIH 9733-UM 1230. (-)-Nicotine di-l-tartrate



MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

1) TF-5.2 (2.7 10.0)

2) TF vs M-0.6 (0.03-15.0)

MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

3) PPQ-1.3 (0.5-3.2)

4) HP-2.2 (1.6-3.0)

MONKEY DATA #ANIMALS STUDY 1. 1, 1, 3,
A. (SDS) Doses (mg/kg/sc) 0.03 0.06 0.125

4 5, 3,
0.25 0.5 0.75

Vehicle-H_2O

STUDY 2. 2, 2, 2,
0.125 0.25 0.5
Vehicle-H_2O

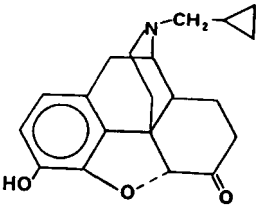
MCV 4194 did not substitute for morphine in the dose range tested.

MONKEY DATA #ANIMALS 1, 2, 3, 2, 1,
B. PPt-Withdrawal) Doses (mg/kg/sc) 0.96 0.48 0.24 0.1 0.06

Vehicle-H_2O

At the 3 higher doses, (-)-nicotine produced restlessness. Other signs such as drowsiness, avoids contact and wet dogs were seen but they were also observed in one monkey receiving H_2O. (-)-Nicotine does not appear to be a specific narcotic antogonist.

MCV 4195-NIH 9735. N-Cyclopropylmethyl-7 8-dihydronormorphinone



MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

1) TF-0.04 (0.035-0.23)

2) TF vs M-0.14 (0.03-0.54)

3) PPQ-0.009 (0.001-0.06)

4) HP-Inactive

5) N-No dose-response

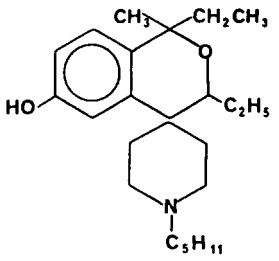
MONKEY DATA #ANIMALS 3, 3, 3, Vehicle-H_2O +
A. (SDS) Doses (mg/kg/sc) 0.15 0.3 0.6 dil, HCl

MCV 4195 did not substitute for morphine. The drug exacerbated withdrawal at all doses tested. Severe tremors were noted in one monkey receiving the highest dose.

MONKEY DATA	#ANIMALS	3 , 3 , 3 , Vehicle-H_2O
B.(PPt-Withdrawal)	Dose (mg/kg/sc)	0.3 0.6 1.2 + dil. HCl

This drug precipitated withdrawal at all doses tested. In one group of monkeys, all receiving MCV 4195 were given morphine to terminate severe withdrawal.

MCV 4198-NIH 9734-UM 1219. dl-Spiro (1,3-diethyl-1-methyl-7-hydroxy-1H-2-benzopyran)-4,4'(1-pentylpiperidine) hydrobromide



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

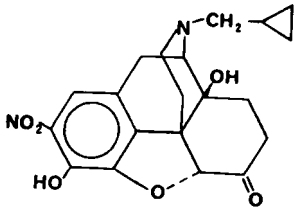
1) TF-Inactive at 1.0 and 30.0

2) TF vs M-6% at 1.0; 32% at 10.0, and 8% at 30.0

3) PPQ-2.5 (1.25-4.81)

4) HP-Inactive

MCV 4199-NIH 9738,2-Nitronaltrexone



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-0% at 0.3; 14% at 3.0; 23% at 10.0; lethal 4/6 at 30.0

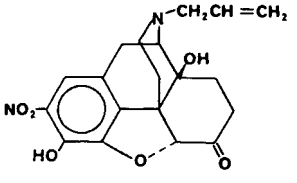
2) TF vs M-21% at 10.0; 27% at 15.0; lethal 6/6 at 30.0

3) PPQ-3.5 (1.4-8.5)

4) HP-3.7 (2.3-5.7)

5) N-5.8 (4-1-8.4)

MCV 4200-NIH 9739 2-Nitronaloxone



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-0% at 1.0, 17% at 10.0, 5/6 died at 30.0

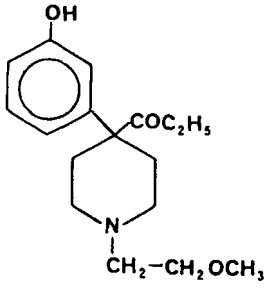
2) TF vs M-3.6 (0.8-16.8)

3) PPQ-3.5 (1.8-6.8)

4) HP-3.1 (2.0-4.8)

5) N-6.0 (4.5-8.0)

MCV 4201-NIH 9740-UM 1220. N-(2-Methoxyethyl)norketobemidone oxalate



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-2.1 (1.3-3.3)

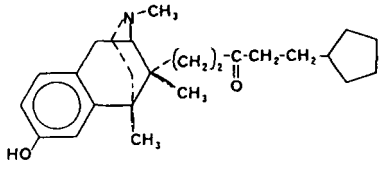
2) TF vs M-0% at 1.0 and 30.0

3) PPQ-0.9 (0.55-1.53)

4) HP-0.73 (0.55-0.98)

5) N-2.1 (1.4-3.1)

MCV 4202-NIH 9751-UM 1228. (2-alpha, 6-alpha,11S)-(+)-1-Cyclopentyl-5-(1,2,3,4,5,6-hexahydro-8-hydroxy-3.6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)-3-pentanone methanesulfonate



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-Inactive at 0.1, 1.0, 10.0, and 30.0

2) TF vs M-6% at 1.0, 4% at 3.0, 10.0 and 17% at 30.0

3) PPC-Inactive 1.0 and 30.0

4) HP-No dose-response

5) N-Inactive to 100.0

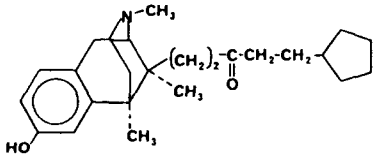
MONKEY DATA	#ANIMALS				
A. (SDS)	Doses (mg/kg/sc)	2 / 10.0	2 / 5.0	2 / 2.5	Vehicle-H_2O

This drug did not substitute for morphine. It may have exacerbated withdrawal. Severe tremors were noted and morphine was given to the monkey in the preliminary study receiving a cumulative dose of 10 mg/kg in 1/2 hour and to another receiving the highest dose in this SDS study to terminate severe withdrawal.

MONKEY DATA	#ANIMALS					
B.(PPt-Withdrawal)	Doses(mg/kg/sc)	1 / 20.0	2 / 10.0	2 / 5.0	1 / 2.5	Vehicle-H_2O

At the two higher doses, MCV 4202 precipitated withdrawal. The onset and duration of action was similar to that of naloxone. The drug is about 400 x less potent than naloxone. Drug supply was exhausted.

MCV 4203-NIH 9752-UM 1229. (2-alpha,6-alpha,11S)-(-)-1-Cyclopentyl-5-(1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6 methano-3-benzazocin 11-yl)-3-pentanone methanesulfonate



MOUSE DATA-ED_{50} (95% C.L.)
(mg/kg/sc)

1) TF-Inactive at 1.0, 10.0 and 30.0

2) TF vs M-0.06 (0.01-0.39) ED$_{50}$ Time Course: 78% at 1 hour 71% at 3 hours, 31% 10 hours and 0% at 30 hours.

3) PPQ-44% at 0.001; 27% at 0.01; 33% at 0.1% at 1.0; 65% at 10.0 and 47% at 30.0

4) HP-No dose-response

5) N-Inactive to 100.0

MONKEY DATA	#ANIMALS					
A. (SDS)	Doses (mg/kg/sc)	1 / 0.015	1 / 0.06	1 / 0.05	1 / 0.1	2 / 0.25

Vehicle-H_2O

MCV 4203 did not substitute for morphine. The drug exacerbated withdrawal. One monkey at the lowest dose had convulsions about 6 hours after the study was started. Another monkey receiving the highest dose appeared sick. Morphine was given after 2 1/2 hours to terminate severe withdrawal but some of the monkeys still vocalized when their abdomens were palpated and had rigid abdomens 9 hours after the start of the experiment in spite of the fact that morphine was given.

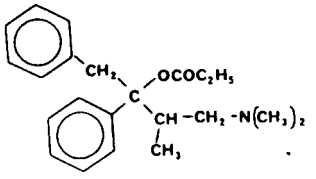
MONKEY DATA	#ANIMALS				
B. (PPt-Withdrawal)	Doses (mg/kg/sc)	2 / 0.008	3 / 0.03	3 / 0.1	1 / 0.125

1 / 0.50, Vehicle-H_2O

The drug precipitated withdrawal signs at all but the lowest dose. The monkey receiving the highest dose was very sick and moved about very slowly for 2 days in spite of repeated doses of morphine. One monkey receiving 0.125 mg/kg and another receiving 0.03 mg/kg still showed withdrawal signs after 2 injections of morphine (3.0 mg/kg). At this dose, morphine may not be an adequate antidote.

MCV 4204-NIH 9757-UM 1231. Dextropropoxyphene hydrochloride
MOUSE DATA-ED_{50} (95% C.L.)-
(mg/kg/sc)

MCV 4204-NIH 9757-UM 1231. (continued) Mouse Data



1) TF--19.4 (15.5-24.5)

2) TF vs M-Inactive at 0.1, 1.0, and 25.0

3) PPQ-2.2 (0.7-6.6)

4) HP-3.8 (2.8-5.2)

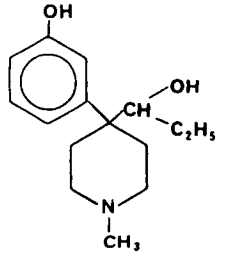
5) N-7.1 (5.3-9.4)

MONKEY DATA (SDS)	#ANIMALS					
	Doses (mg/kg/sc)	1, 10.0	2, 5.0	3, 2.5	2, 0.6	1, 0.3

Vehicle-H_2O

At the highest dose, MCV 4204 substituted completely and briefly (1 hour) for morphine. The drug behaved similarly in 1 of 2 animals receiving 5.0 and 2 of 3 animals receiving 2.5 mg/kg.

MCV 4205-NIH 9771. 4-(1-Hydroxypropyl)-4-m-hydroxyphenyl-1-methylpiperidine



MOUSE DATA-ED_{50} (95% C.L.)-(mg/kg/sc)

1) TF-0% at 20.0 and 11% at 30.0

2) TF vs M-0% at 0.1; 20% at 1.0 and 12% at 30.0

3) PPQ-0% at 0.1; 29% at 1.0 and 11% at 30.0

4) HP-No dose-response

MONKEY DATA (SDS)	#ANIMALS					
	Doses (mg/kg/sc)	1, 20.0	3, 10.0	2, 5.0	2, 2.5	Vehicle-Lactic Acid and H_2O

In the dose range studied, MCV 4205 does not substitute for morphine.

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Annual Report: Evaluation of New Compounds for Opioid Activity (1980)

J. H. Woods, F. Medzihradsky, C. B. Smith, A. M. Young, and H. H. Swain

The flow of new compounds through the evaluation programs at The University of Michigan (UM) and the Medical College of Virginia (MCV) is coordinated by Dr. Arthur E. Jacobson, Medicinal Chemistry Section, NIAMDD, 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 ANALGESIA tests (see Table I below).

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.

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

The single dose suppression test (SDS) determines the ability of a drug to suppress the signs of abstinence in monkeys which have been made physically 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 abstinence syndrome in non-withdrawn (NW) morphine-dependent monkeys. Non-dependent monkeys (Normals) are used to determine whether the acute effects of the test drug are reversible by nalorphine or naloxone. In a primary addiction study (PAS) non-dependent monkeys receive the test drug every six hours for 30 days to determine whether abstinence signs will appear when the animals are challenged with an antagonist or when drug administration is discontinued.

Details of these techniques have been presented in the ANNUAL REPORT to the Committee in 1963 (Minutes of the 25th Meeting).

SELF-ADMINISTRATION BY MONKEYS

The compounds were examined in monkeys which had been conditioned 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 elicited by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response in its presence turns off the fixed-ratio light and delivers a five-second intravenous drug injection in the presence of another light that is illuminated during drug delivery. After each injection, a ten-minute timeout condition is in effect, during which responses have no programmed consequence and no lights are illuminated. Each of the two daily sessions consists of 13 injections or 130 minutes, whichever occurs first. Other details of the procedure and initial findings with a variety of narcotics are given in a previous report (Woods, 1977, Committee Report, pages 420-437). Additional background material is available from Dr. Woods.

Doses of the drugs are described in terms of moles/kg/injection, to facilitate direct comparisons among drugs. Duplicate observations of codeine (7.5×10^{-5} mol/kg/injection; 0.32 mg/kg/injection) and of saline are obtained for each monkey. A saline substitution is conducted before and after the series of observations on a test drug; the rates of codeine-reinforced responding are obtained by a random sampling of two sessions interpolated between the drug-substitution sessions. These data are represented in the following graphs with individual symbols for each of the monkeys; in addition, using the same symbols, the mean of duplicate observations is given for the doses studied 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 mean for codeine and +3 standard errors of the mean for saline. In all cases, the rates of responding given are those calculated during the fixed-ratio portion of each session.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Details of the binding assay were described in the 1978 ANNUAL REPORT. Briefly, aliquots of a membrane preparation from rat cerebrum are incubated with ^{3}H-etorphine in the absence and presence of 150 mM NaCl, and in the presence of different concentrations of a given opioid drug under investigation. Stereospecific, i.e., opioid-receptor related, binding of etorphine is determined and the inhibitory potency of the drug is obtained from log-probit plots of the data. Values obtained with this method for some representative opioid drugs are as follows:

DRUG	EC_{50} (nM)		
	+NaCl	-NaCl	+Na/-Na
Naltrexone	2.0	7.9	0.25
Naloxone	9.1	31.6	0.29
Nalorphine	20.0	51.3	0.39
Cyclazocine	3.6	6.4	0.56
Levallorphan	5.5	7.0	0.79
Dextrorphan	18400	14000	1.32
Levorphanol	21.4	15.4	1.39
Codeine	34700	17800	1.95
l-Pentazocine	174.0	85.1	2.04
d-Pentazocine	6190	8660	0.71
Morphine	142.0	60.2	2.36

NOTE: Binding data for a number of other compounds are included in the 1978 and 1979 ANNUAL REPORTS.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA PIG ILEUM AND MOUSE VAS DEFERENS PREPARATIONS

Submitted drugs are evaluated on two smooth muscle preparations, the details of which were described in the 1978 ANNUAL REPORT. Shown in the following pages are the EC_{50}'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 seems to be more effective against "kappa" than against "mu" drugs). The maximum depression of the electrically induced twitch in each of these preparations is also indicated.

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 II.

TABLE I

MOUSE ANALGESIA. Before submission to The University of Michigan, all compounds are evaluated for analgesic activity by Dr. Arthur E. Jacobsord. Shown below are comparative data (ED_{50} mg/kg) (95% Confidence Interval) from Hot Plate[H-C] and Nilsen assays. umo/lkg

Compound NIH #	HOT PLATE (sc, mg/kg) (sc, umol/kg)	HOT PLATE (oral, mg/kg) (oral, umol/kg)	NILSEN (sc, mg/kg) (sc, umol/kg)	NILSEN (oral, mg/kg) (oral, umol/kg)
Morphine sulfate NIH 0001	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.HBr 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)

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 NM 8503	No dose response			
Naloxone. HCl NIH 7890	No dose response			

No antinociceptive activity in hot plate assay: Phenobarbital, amobarbital, diazepam, meprobamate, mescaline, oxazepam, flurazepam.

Chlorpromazine.HCl	1.1 (0.9-1.5) 3.2 (2.4-4.2)			

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TABLE II

SUMMARY OF TESTS PERFORMED

COMPOUND NUMBER UM	NIH	MCV	CHEMICAL CLASS	SDS	NW	Normals	Self-Adm.	GPI	MVD	Bind.	PAS
909	8735A	4189	Benzomorphan	(+)	-	-	(+)	-	-	-	+
941	8791		Butorphanol	(+)	(+)	-	(+)	-	-	-	+
1125A	9343A	4103	Phenylpiperidine	(+)	(+)	-	-	-	-	-	+
1144	9048	4041	Miscellaneous	+	-	-	-	-	-	-	-
1151	9549	4155	Clonidine	+	-	+	+	+	+	+	-
	(9571)	(4183)	" "								
1159	9513		Cannabinoid	(+)	(+)	(+)	+	-	-	-	-
1167	9538	4177	Dioxamorphinan	+	+	-	+	+	+	+	-
1168	9539		Oxamorphinan	(+)	(+)	-	(+)	(+)	(+)	(+)	+
1173	9550		Miscellaneous	+	-	-	+	-	-	-	-
1184	9629		Naloxone quat.	+	+	-	+	-	-	-	-
1185	9630		Naltrexone quat.	+	+	+	-	-	-	-	-
1189	9463		Miscellaneous	+	+	-	+	-	-	-	-
1190	9627		Miscellaneous	+	-	-	-	-	-	-	-
1195	9637		sec-Butylnormorphine	+	-	-	-	+	+	+	-
1196	9648		Ketobemidone	+	-	+	-	-	-	-	-
1199	9673		Miscellaneous	+	-	+	-	-	-	-	-

TABLE II (cont.)

COMPOUND NUMBER UM	NIH	MCV	CHEMICAL CLASS	SDS	NW	Nor-mals	Self-Adm.	GPI	MVD	Bind	PAS
1202	9701		Mercaptomorphine	-	-	-	-	+	+	+	-
1203	9702		Mercaptocodeine	-	-	-	-	+	+	+	-
1204	9703		Amidocodeine	-	-	-	-	+	+	+	-
1205	9704		Amidocodeine	-	-	-	-	+	+	+	-
1206	9705		Amidomorphine	-	-	-	-	+	+	+	-
1207	9706		Aminocodeine	-	-	-	-	+	+	+	-
1208	9707		Chlorocodeinone	-	-	-	-	+	+	+	-
1209	9708		Chloromorphinone	-	-	-	-	+	+	+	-
1210	9709		Bromomorphinone	-	-	-	-	+	+	+	-
1211	9712		Galanthamine	-	-	-	-	+	+	+	-
(136)	(7380)										
1213	9725	4188	Peptide	+	-	-	+	+	+	+	-
1214	9726	4171	Sufentanil	+	-	-	+	+	+	+	-
1215	9729	4193	Phenylpiperidine	+	+	-	-	+	+	+	-
1218	9585		Ketobemidone	+	-	-	-	-	-	-	-
1219	9734	4194	Miscellaneous	+	-	-	-	-	-	-	-
1220	9740	4201	Ketobemidone	+	-	+	-	-	-	-	-
1221	9741		Ketobemidone	+	-	-	-	-	-	-	-

TABLE II (cont.)

COMPOUND NUMBER UM	NIH	MGV	CHEMICAL CLASS	SDS	NW	Nor-mals	Self-Adm.	GPI	MVD	Bind.	PAS
1222	9742		Miscellaneous	+	-	-	-	-	-	-	-
1228	9751	4202	Benzomorphan	-	-	-	-	+	-	+	-
1229	9752	4203	Benzomorphan	-	-	-	-	+	-	+	-
1230	9733	4194	Nicotine	+	-	-	-	+	+	+	-
1231	9757	4204	Propoxyphene	+	-	+	-	+	+	+	-
1232	9769		Ketobemidone	+	-	-	-	-	-	+	-
1233	9770		Ketobemidone	+	-	-	-	+	+	+	-
1237	9789		Ketobemidone	+	-	-	-	-	-	+	-
1242	9576A	4157	Miscellaneous	+	-	-	-	+	+	+	-
1258	9624	4175	Benzomorphan	-	-	-	+	-	-	-	-

SDS = Single-dose suppression of abstinence signs in morphine-dependent monkeys

NW = Attempted precipitation of abstinence in non-withdrawn, morphine-dependent monkeys

Normals = Attempted reversal by nalorphine and naloxone of effects in non-dependent monkeys

Self-Adm. = Test of reinforcing properties in monkeys which normally self-administer codeine

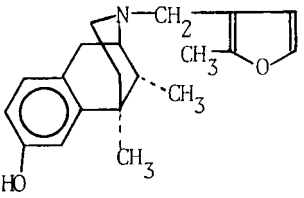
GPI = Suppression of twitch in electrically driven guinea-pig ileum preparation

MVD = Suppression of twitch in electrically driven mouse vas deferens preparation

Bind. = Stereospecific displacement of ^{3}H-etorphine in membrane preparation from rat cerebrum

PAS = Primary addiction study in monkeys

UM 909 NIH 8735A MCV 4189
PRIMARY ADDICTION STUDY



2-(2-Methyl-3-furylmethyl)-2' -hydroxy-5,9 alpha-dimethyl-6,7-benzomorphan methanesulfonate

In single-dose-suppression studies (see 1972 ANNUAL REPORT), this compound produced no suppression of abstinence signs in morphine-dependent Rhesus monkeys, but it caused severe, short-lasting CNS depression at a dose of 8.0 mg/kg. In mouse analgesia studies, it had a potency approximately one-half that of morphine, with an ED50 of 2.2 (1.7-2.8) mg/kg.

Animals. Rhesus monkeys numbered 115A, 205A and 1123 were used in this sutdy. Throughout the study, the weights of these monkeys remained essentially constant.

Dosage schedule. The initial dose of UM 909 was 2.0 mg/kg, given subcutaneously every six hours. On the third day of the study, this was raised to 4.0 mg/kg and on Day 8 it was raised again to 8.0 mg/kg every six hours. On Day 18, monkey number 1123 received one dose of 16 mg/kg and, twenty minutes after the injection, the animal convulsed and was treated with pentobarbital. Thereafter, the dose for all three animals remained at 8.0 mg/kg/injection. On the 23rd day, the injection interval was reduced from six hours to three hours for the remainder of the study. On Day 36, the administration of UM 909 was discontinued abruptly.

Acute effects. UM 909 caused signs of CNS depression. The monkeys became moderately ataxic, showed muscle weakness and decreased body movement. They had blank facial expressions and stared into space. Their pupils were dilated; their respiration was not depressed. All of these effects were relatively short-lasting. Initially the signs were gone within three hours of the injection, but as tolerance developed, they were hard to detect after two hours or even less. Tolerance was also apparent from the decreasing severity of the CNS depression as a dose was repeated.

The skin on the animals' backs became hardened and showed increased bleeding at injection sites as the study progressed. (This local effect has been observed previously with other benzomorphan drugs.)

Physical dependence. When UM 909 was injected every six hours, the development of physical dependence was minimal. On the 15th day of the study, the injection of nalorphine (2.0 mg/kg) reversed the acute effects of the immediately preceding dose of UM 909 (ataxia and CNS depression) but precipitated only the mildest of abstinence

339-844 0 - 81 - 23

signs. On the 17th day, a challenge with 2.0 mg/kg of naloxone produced only slightly more severe abstinence, characterized by retching and vomiting, apprehension and irritability to handling.

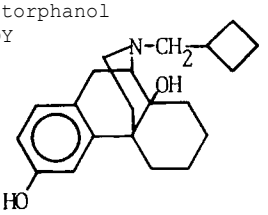
On an every-three-hour injection schedule (initiated on Day 23) the physical dependence became more marked, so that the nalorphine challenge on Day 28 precipitated mild abstinence and the naloxone challenge on Day 30 produced moderately severe signs. These latter included vomiting, yawning, irritability, prostration and abdominal tenderness but not the abdominal guarding and rigidity which would have been seen in morphine-dependent animals.

An additional challenge was performed on Day 32 when the animals were given a dose of an antagonist which structurally is almost identical to the agonist DM 909. known variously as UM 979, NIH 8859 and Mr 1452-MS, this antagonist lacks the 2-methyl group which is present on the furyl ring of UM 909, and in small doses it precipitates abstinence signs in morphine-dependent monkeys. There has been speculation that UM 979 is preferentially effective at so-called "kappa" receptors, and therefore it might be especially active in antagonizing the effects of UM 909, which behaves like a kappa agonist. However, the abstinence signs precipitated by the challenge with UM 979 were only mild in intensity.

Upon the abrupt discontinuation of UM 909 administration, mild abstinence signs appeared, with their peak intensity observed at 12 hours after the last dose of the drug, and disappearing completely over a period of 6 - 8 days. As was the case with precipitated abstinence, abdominal guarding and rigidity were absent from the syndrome.

Summary. UM 909 is a drug which neither suppresses nor precipitates the signs of abstinence in a morphine-dependent Rhesus monkey. It produces CNS-depressant signs of relatively brief duration. Tolerance develops to these effects upon repeated administration of the drug. In one animal, which had become partially tolerant to the depressant effects of 8.0 mg/kg of UM 909, a single dose of 16 mg/kg produced convulsions. Physical dependence developed to only a minimal degree when the drug was given every six hours, and to a moderate degree when administered every three hours. A structurally related antagonist, known as UM 979, was less effective than naloxone in precipitating the abstinence syndrome. The abstinence signs which followed either antagonist administration or the abrupt withdrawal of the drug differed somewhat from those seen during morphine withdrawal -- in particular, abdominal guarding and rigidity were not seen.

UM 941, NIH 8791, Butorphanol
PRIMARY ADDICTION STUDY



(-)-N-Cyclobutylmethyl-3,14-dihydroxymorphinan tartrate

In single-dose suppression studies (see 1973 ANNUAL REPORT), this compound caused mild exacerbation of morphine abstinence signs, when the drug was given in a dose of 6.4 or 12.8 mg/kg. However, in the non-withdrawn, morphine-dependent monkeys, a dose of 6.4 mg/kg did not precipitate any abstinence signs. The highest dose tested in withdrawn, dependent animals was 25.6 mg/kg, which caused convulsions.

Animals. Rhesus monkeys numbered 1186, 1194 and 1195 were used in this study. Throughout the investigation, the animals maintained essentially constant weight and they suffered no apparent ill-effects from the study.

Dosage schedule. The drug was administered subcutaneously every six hours. The starting dose, given on Days 1 through 3, was 0.8 mg/kg. This was raised to 1.6 mg/kg for Days 4 through 11; it was 3.2 mg/kg on Days 12 through 18; finally, a dose of 6.4 mg/kg was given to the animals every six hours from Day 19 through Day 42. On the 43rd day of the study, drug administration was abruptly discontinued.

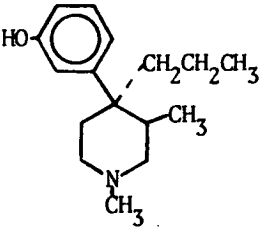
Acute effects. The starting dose of UM 941 caused marked CNS depression with muscle weakness, ataxia and body sag. When the animals were handled, they showed little or no aggression or irritability. When left alone, they tended to stay in one place, with little tendency to move around in the cage. Pupil size was increased and, likewise, respiration increased. Tolerance, as evidenced by the effects of UM 941 becoming less intense and shorter in duration, developed to the actions of the drug within a few days.

Physical dependence. On the 14th day of the study, the monkeys were challenged with a dose of 2.0 mg/kg of nalorphine, which produced mild abstinence signs which included a general restlessness and irritability, a decrease in pupil size, scratching, stretching, peculiar postures, quarreling and salivation. Interestingly, the animals did not show any abdominal tenderness or cramps, though they did tend to hold their abdomens. On a scale of 1 (very mild) to 8 (very severe), these abstinence signs were graded as 1. A naloxone challenge (2 mg/kg) on the 16th day produced essentially the same withdrawal signs (including the absence of the usual abdominal tenderness), but the withdrawal was more severe (grade = 4). The nalorphine challenge was repeated on the 31st day, and the signs

were at least as mild as those seen on the 14th day. The repeat of the naloxone test on Day 36, on the other hand, produced signs which were more severe than those of Day 16 (grade = 6); the monkeys were very irritable, had severe retching and vomiting and displayed the "half-retch/half-yawn" behavior which has been seen previously in animals withdrawing from cyclazocine-like drugs. Abrupt withdrawal of the drug on the 43rd day of the study produced abstinance signs which were intermediate in severity between those seen after nalorphine and those precipitated by naloxone; they were rated as grade = 3. The withdrawal signs peaked in intensity at 30-36 hours after the last dose of UM 941 and had disappeared after 96 hours.

Summary. UM 941 behaves like an effective narcotic agonist, a weak narcotic antagonist or a convulsant, depending upon the circumstances of its administration. In the 14-hour-withdrawn, morphine-dependent monkey, the agonist activity of the drug is not apparent; instead, its antagonist properties are shown by a mild exacerbation in the severity of the abstinence syndrome. In the normal (non-dependent) monkey, UM 941 produces narcotic-like CNS depression, and tolerance and physical, dependence develop upon repeated administration of the drug. The unusual characteristics of this drug include (1) the markedly greater severity of the naloxone-induced abstinence, compared to the nalorphine-induced withdrawal signs, and (2) the absence of abdominal tenderness during withdrawal.

UM 1125A, NIH 9343A
PRIMARY ADDICTION STUDY



m-(1,3-Dimethyl-4-propyl-4-piperidyl)phenol hydrobromide

In single-dose-suppression studies in morphine-dependent Rhesus monkeys, this drug caused mild CNS depression in doses up to 40 mg/kg/; at 80 mg/kg it caused convulsions (see 1978 ANNUAL REPORT) - It neither suppressed nor precipitated the signs of morphine abstinance. In the non-dependent monkey, the CNS depression which it produced was not reversed by either nalorphine or naloxone.

Animals. Rhesus monkeys numbered 1126, 1127 and 1133 were used in study. All three animals tolerated the procedures well and maintained their body weights throughout. The animals developed abscesses on their backs at the sites of subcutaneous injections.

Dosage schedule. The animals received 10 mg/kg of UM 1125A every six hours for the first seven days of the study; 20 mg/kg four

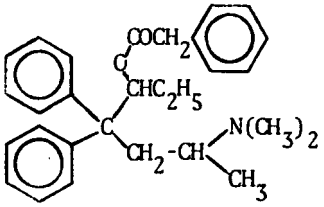
times each on Days 8 through 28, after which drug administration was abruptly discontinued. There were problems in putting and keeping the drug in solution. For the 10 mg/kg dose, it was dissolved in 1/3 propylene glycol and 2/3 water. When the dose was raised to 20 mg/kg, the higher concentration of drug would not stay in solution in the propylene glycol, even when the solution was kept warm, and once it had come out of solution, it would not go back into solution with rewarming. Emulphor EL 620 diluted with water to 1/3 strength proved to be more satisfactory. The drug would stay in solution for 2-3 days, and would re-enter solution when rewarmed. This 33% Emulphor solution was used as the vehicle for the remainder of the study.

Acute effects. UM 1125A caused CNS depression. The animals showed marked ataxia and motor incoordination. At times they would stare wide-eyed, and at other times they would doze and appear to be mildly stuporous. Strong stimuli were needed to produce any reaction on the part of the animals. There were slight tremors and perhaps some slight increase in respiratory rate. Upon repeated administration of the drug, the signs became less prominent, suggesting development of tolerance.

Physical dependence. On the 14th day of the study, the animals were challenged with nalorphine, 2.0 mg/kg subcutaneously. No abstinence signs were produced, although there may have been some slight increase in the extent of CNS depression. Nalorphine challenge was repeated on the 21st day, and again there was no precipitation of abstinence signs of any consequence. Naloxone was used to challenge the monkeys on the 16th and again on the 23rd days of the study. On the former occasion, a dose of 2.0 mg/kg produced mild abstinence signs, scored between grades 2 and 3 on the Seevers scale, and consisting of generalized irritability, apprehension, restlessness and nausea and retching. There was a slight increase in respiratory rate. The second naloxone challenge produced similar but slightly more severe signs, scored between grades 3 and 4. When the administration of UM 1125A was abruptly discontinued on the 28th day of the study, as abstinence syndrome appeared which was not typical of withdrawal from morphine and related drugs, though it had enough signs in common with morphine abstinence that a Seevers score of 4 could be used to describe its-peak intensity. The peak occurred between the 60th and 66th hours after the last dose of UM 1125A, and signs were still visible for at least 210 hours. The withdrawal syndrome was characterized by generalized irritability, restlessness and apprehension. The animals held their abdomens and appeared to be nauseated. They showed intention tremors or shivering. There was questionable tenderness of the abdomen.

Summary. This is a drug which neither suppresses nor precipitates abstinence in morphine-dependent monkeys, and whose direct effects of CNS depression are not antagonized by nalorphine or naloxone. Upon chronic administration, it produced CNS depression and upon discontinuation there was mild-to-moderate abstinence, which was not typical of a morphine-like drug. Withdrawal signs were precipitated by naloxone, but not nalorphine, after 14-21 days of UM 1125A.

UM 1144 NIH 9048 MCV 4041



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 4.5 (3.2-6.4)

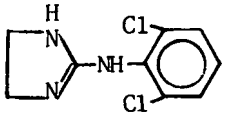
Nilsen: ---

alpha-4,4-Diphenyl-6-dimethylamino-3-heptanol phenylacetate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

In the doses tested, the drug produced no behavioral effects on the animals, but it causes lumps at the injection sites, and one of these lumps developed into an abscess. Therefore, higher doses were not tested. Doses tested: SDS, 2.0, 4.0, 8.0. Vehicle: water, 33% propylene glycol for highest dose.

UM 1151 NIH 9549 & 9571 MCV 4155 & 4184 Clonidine



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.98 (0.66-1.46)

Nilsen: ---

2-(2,6-Dichloroanilino)-2-imidazoline hydrochloride

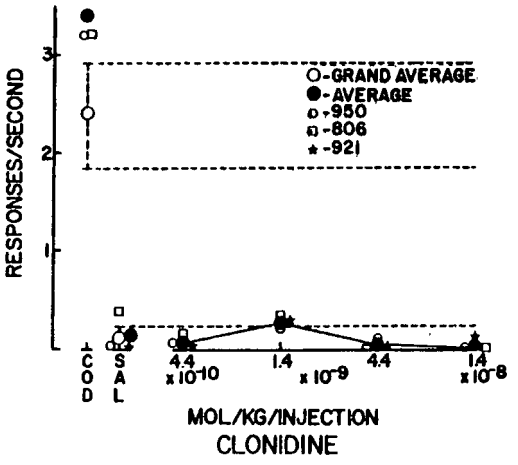
PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

Clonidine neither suppresses nor precipitates morphine abstinence signs in dependent monkeys. It causes a dose-dependent CNS depression, not like that of morphine, but characterized by muscle weakness, ataxia and apparent dysphoria, which is not reversed by naloxone and may actually be made more severe by nalorphine. Doses tested: SDS, 0.005-0.16, Normals, 0.16 mg/kg. Vehicle: water.

DRUG DISCRIMINATION IN PIGEONS AND MONKEYS

In pigeons trained to discriminate morphine or pentobarbital from saline, clonidine evoked drug-appropriate responding in one of four birds at doses that reduced rates of responding that were maintained by food delivery. In monkeys trained to ethylketazocine, clonidine brought about intermediate responding in three of four animals, with the fourth monkey placing all of its responding on the saline-appropriate key. Apparently, clonidine has some interoceptive components that are somewhat similar to each of the above compounds, but not enough for it to be classified as equivalent to any.

SELF-ADMINISTRATION BY MONKEYS



Clonidine was studied over a range of doses from 0.0001-0.003 mg/kg/inj in monkeys trained to self-inject codeine (0.32 mg/kg/inj). Clonidine maintained rates of self-injection no higher than those maintained by saline in all three animals.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

Clonidine was inactive in concentrations of 2 µl in the presence or absence of 150 nM NaCl.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

Clonidine is a potent agonist which is not blocked by either naltrexone or UM 979.

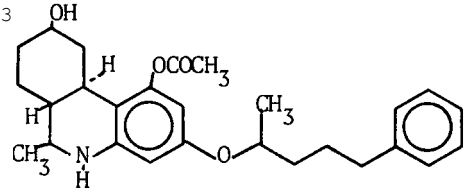
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

The actions of clonidine are blocked by naltrexone but not by UM 979. When the vasa deferentia were isolated from mice treated repeatedly with morphine, there was tolerance to the effects of morphine and a small degree of cross tolerance to those of clonidine.

SUMMARY

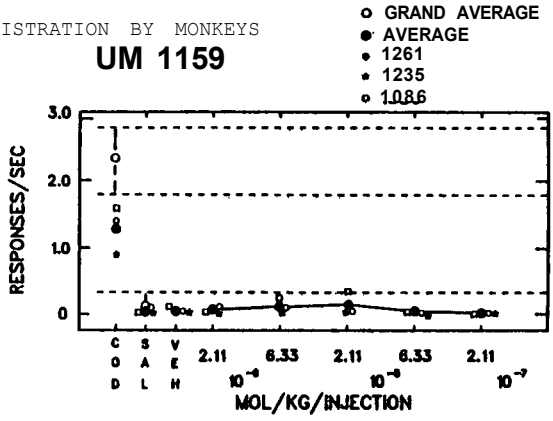
The data suggest that on the guinea-pig ileum clonidine does not exert its effects through a morphine-like mechanism, while on the mouse vas deferens there may be some interaction between clonidine receptors and morphine receptors. The actions of clonidine in the behavioral preparations point to non-morphine-like sedative properties which are not reversed by naloxone. Nevertheless, these data show that the drug is very potent and has strong behavioral effects.

UM 1159 NIH 9513



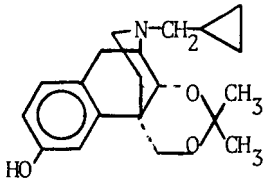
dl-trans-5,6,6a beta,7,8,9,10,10a alpha-Octahydro-1-acetoxy -9 beta-hydroxy-6 beta-methyl-3-(5-phenyl-2-pentyloxy)- phenanthridine hydrochloride

SELF-ADMINISTRATION BY MONKEYS



UM 1159 was dissolved in a mixture of Emulphor and ethanol and diluted with saline. It was studied over a dosage range of 0.001-0.1 mg/kg/injection. Thus, the highest dose tested was close to that which would have produced directly observable behavioral effects. The drug failed to maintain self-injection responding at rates above those of saline.

UM 1167 NIH 9538 MCV 4177



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.21 (0.18-0.26)

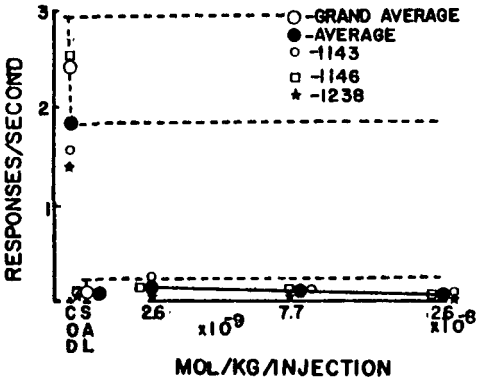
Nilsen: ---

(-)-17-Cyclopropylmethyl-7,7-dimethyl-3-hydroxy-6,8-dioxamorphinan d-tartrate methanolate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

A potent narcotic agonist which, for any particular degree of abstinence suppression, produces a remarkable amount of CNS depression. There is no indication that this drug has any antagonist properties. Doses tested: SDS, 0.025-0.20 mg/kg; NW, 0.1 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY RHESUS MONKEYS



UM 1167

Three doses of UM 1167 were studied (2.6×10^{-9} - 2.6×10^{-8} M/kg). None of these doses maintained self-injection responding above saline. A few observations were obtained at higher doses; these also produced very low self-injection rates. These higher doses reduced subsequent codeine self-injection.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	0.87	1.17	0.75

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone	1.74×10^{-9}
	After naltrexone, 10^{-7}M	5.80×10^{-7}
	After UM 979, 10^{-7}M	1.40×10^{-8}

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

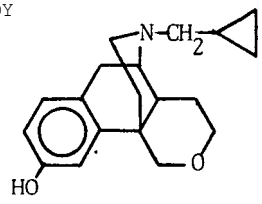
EC_{50} (M)	Drug alone	8.6×10^{-10}
	After naltrexone, 10^{-8}M	2.4×10^{-9}
	After UM 979, 10^{-8}M	6.3×10^{-10}

SUMMARY

UM 1167 is an unusual drug in that it resembles morphine in some respects but not in others. It is a potent agent for displacing etorphine and for inhibiting the electrically induced twitch in the guinea-pig ileum and mouse vas deferens preparations. Depending on the preparation employed, the compound is 10 to 50 times as potent as morphine. The ability of naltrexone and UM 979 to reverse the actions of UM 1167 on the guinea-pig ileum suggests a morphine-like action; however, the drug appears to have a different mechanism of action in the mouse vas deferens, where these antagonists are ineffective.

The acute behavioral signs produced by UM 1167 were reversed by both nalorphine and naloxone. The ataxia and sedation produced by the compound suggest an ethylketazocine-like component in addition to morphine-like actions. This is the first compound which we have studied which was not self-injected by monkeys even though it completely suppressed the abstinence signs in morphine-dependent animals.

UM 1168 NIH 9539
PRIMARY ADDICTION STUDY



17-Cyclopropylmethyl-3-hydroxy-6-oxamorphinan tartrate

In single dose suppression studies, this drug behaved like an opioid antagonist, approximately equal in potency to, but longer lasting than nalorphine. It was not self-administered by monkeys which had been trained to self-administer codeine. In competing for etorphine-binding sites in a membrane preparation from rat brain, the drug showed a high affinity and an intermediate sodium-response ratio. UM 1168 depressed the twitch in electrically driven preparations of the isolated guinea pig ileum and mouse vas deferens, and this depressant activity was not greatly antagonized by naltrexone. The drug is a potent analgesic in the mouse hot-plate test and the phenylquinone-writhing test but not in the tail-flick test. (See 1979 ANNUAL REPORT of the Drug Abuse Basic Research Program of The University of Michigan and the comparable report by the Medical College of Virginia in the Proceedings of the Forty-first Annual Scientific Meeting of the Committee on Problems of Drug Dependence.)

Animals. In this study, Rhesus monkeys numbered 234A, 279A and 392A were used.

Dosage schedule. The initial dose of UM 1168 was 0.1 mg/kg subcutaneously, and because this produced prolonged effects, the dose was given only every 12 hours (instead of every six hours, which is usual in Primary Addiction Studies). On the eighth day, the dose was doubled to 0.2 mg/kg every 12 hours. By this time the animals had developed considerable tolerance to the effects of the drug, and so the dosing interval was reduced to the normal six hours on the eleventh day of the study. On the 17th day, the dose was doubled again, to 0.4 mg/kg every six hours; 0.8 mg/kg every six hours was begun on the 23rd day; and 1.6 mg/kg every six hours was given from the 25th day on. Drug administration was discontinued abruptly on the 32nd day of the study.

Acute effects. Initially, UM 1168 produced marked, long-lasting CNS depression, characterized by body-sag, ataxia, dozing, pupil dilatation and very little in the way of facial expression. These signs were maximal from the second to the eighth hour after drug injection

and were still apparent at 12 hours. For the first day or two, the monkeys ate very little food, presumably because of the continuous CNS depression.

By the eighth day, the signs were significantly less prominent, even when the dose had been doubled from 0.1 to 0.2 mg/kg every 12 hours. There was still some body sag apparent when the animals were sitting and very mild ataxia when they walked.

Subsequently, the dosage interval was reduced to six hours and the dose was raised to 0.4, 0.8 and finally 1.6 mg/kg, but the signs remained mild, with slight pupil dilatation and minimal body sag. It was apparent that rather marked tolerance had developed to the effects of UM 1168.

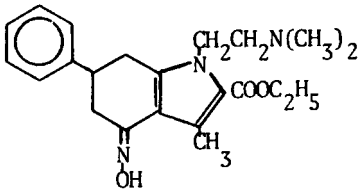
Physical dependence. On the 15th day, the monkeys were challenged with nalorphine, 2 mg/kg, at a time when they were showing mild sedation from the preceding UM 1168 dose. The antagonist reduced that sedation somewhat and produced very mild abstinence signs (approximately Grade 1 on the Seevers scale) of yawning and slight irritability to handling but no abdominal tenderness. Naloxone challenge (2 mg/kg) , performed on the 17th day, produced moderate abstinence signs (approximately Seevers Grade 3). There was yawning, retching, apprehension, restlessness, dyspnea, and the animals lay on their sides. As with the nalorphine challenge, naloxone produced no abdominal tenderness or rigidity.

Repeated challenges two weeks later produced milder abstinence signs. The 29-day nalorphine produced restlessness and apprehension, which was graded as less than 1 on the Seevers scale. The naloxone challenge on Day 31 produced Grade 2 signs including restlessness, apprehension, increased respiration, nausea, yawning, retching and the peculiar "half yawn-half retch" sign that has been seen in withdrawal from nalorphine, cyclazocine and some of the so-called "kappa" agonists.

Abrupt withdrawal began on the 32nd day, and once again the signs were very mild, considering the magnitude of the tolerance which had developed at UM 1168 at that time. The peak occurred at approximately 18 hours after the last dose of UM 1168, and was no more than Seevers Grade 1 in any of the three monkeys.

Summary. UM 1168 is a potent narcotic antagonist which has a significant component of ethylketazocine-like agonist activity (kappa activity). It produces marked, relatively prolonged CNS depression, but tolerance develops rapidly to this action. The abstinence signs, produced either by abrupt withdrawal or challenge with nalorphine or naloxone, are much milder than might have been expected on the basis of the marked tolerance development which this drug showed.

UM 1173 NIH 9550



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 5.5 (3.6-8.2) SC
5.4 (3.9-7.5) oral

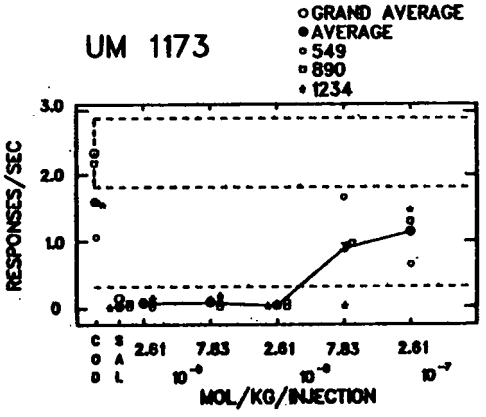
Nilsen: ---

dl-1-(2-(Dimethylamino)ethyl)-6,7-dihydro-3-methyl-4-oxo-6-phenylindole-2-carboxylic acid ethyl ester (E) oxime

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

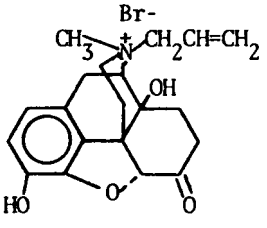
This drug is a narcotic agonist, somewhat less potent and shorter-acting than morphine. Doses tested: SDS, 1.5, 3.0, 6.0 mg/kg. Vehicle: 50% dilute HCl, 50% propylene glycol, heated.

SELF-ADMINISTRATION BY MONKEYS



This drug was self-administered by all three monkeys. Higher doses were not tested due to solubility problems.

UM 1184 NIH 9629



Quaternary Naloxone
(Naloxone methobromide)

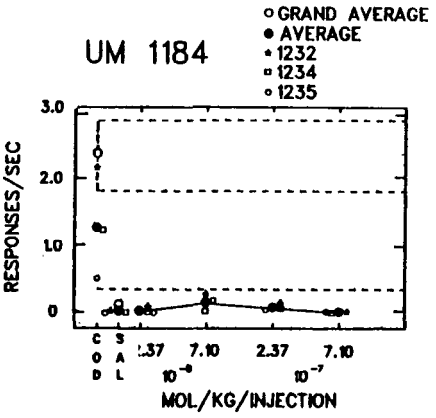
MOUSE ANALGESIA, ED_{50} (mg/kg)

Inactive to 100 mg/kg

PHYSICAL DEPENDENCE IN MONKEYS

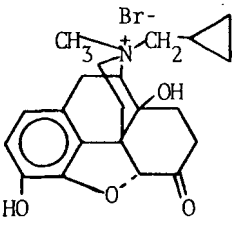
A morphine antagonist, less potent and shorter acting than naloxone, which probably has some agonist properties. Doses tested: SDS, 1.0 mg/kg; NW, 1.0, 2.0, 4.0 mg/kg. Vehicle: water

SELF-ADMINISTRATION BY MONKEYS



No dose of the drug was self-administered.

UM 1185 NIH 9630



Quaternary naltrexone
(Naltrexone methobromide)

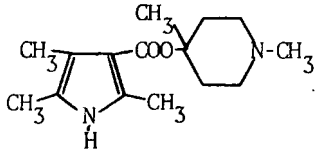
MOUSE ANALGESIA, ED_{50} (mg/kg)

Insufficiently active to assay

PHYSICAL DEPENDENCE IN MONKEYS

This compound was tested over a wide range of doses, but it was neither a narcotic agonist or a narcotic antagonist. It caused very slight CNS depression. Doses tested: SDS, 1.0-16 mg/kg; NW, 1.0-32 mg/kg; normals, 16 mg/kg. Vehicle: water.

UM 1189 NIH 9463



1,4-Dimethyl-4-piperidinol (2,4,5-trimethylpyrrole-3-carboxylate) hydrochloride

MOUSE ANALGESIA, ED_{50} (mg/kg)

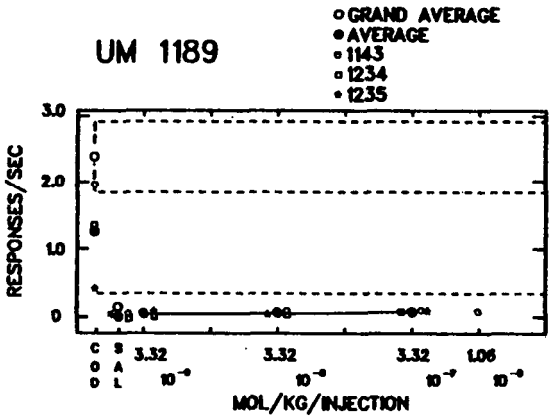
Hot Plate: 4.6 (3.3-6.4)

Nilsen: 6.0 (4.5-7.9)

PHYSICAL DEPENDENCE IN MONKEYS

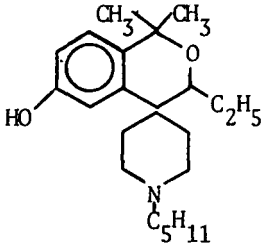
It neither suppresses nor precipitates the signs of morphine abstinence, but at 10 mg/kg it caused the monkeys to appear pre-convulsive, so higher doses were not tested. Doses tested: SDS, 2.5-5.0 mg/kg; NW, 5.0-10 mg/kg. Vehicle: water

SELF-ADMINISTRATION BY MONKEYS



This drug was not self-injected at any tested dose.

UM 1190 NIH 9627



dl-Spiro ((1,1-dimethyl-3-ethyl-7-hydroxy-1H-2-benzopyran)-4,4'-(1-pentylpiperidine)) hydrobromide

MOUSE ANALGESIA, ED_{50} (mg/kg)

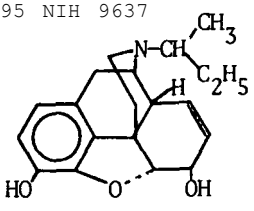
Insufficiently active for assay

PHYSICAL DEPENDENCE IN MONKEYS

At the doses tested, the drug neither suppressed nor precipitated the signs of morphine abstinence. It caused slight CNS depression.

Doses tested: SDS, 2.5-10 mg/kg
Vehicle: 66% propylene glycol

UM 1195 NIH 9637



S-N-sec-Butylnormorphine

MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 15.0 (11.3-19.8)

Nilsen: ---

PHYSICAL DEPENDENCE IN MONKEYS

At the doses tested, the compound neither suppressed nor precipitated the signs of morphine abstinence. The highest dose tested caused tremors and other pre-convulsive signs, but otherwise the compound had very little effect upon the animals Doses tested: SDS, 5.0-40 mg/kg. Vehicle: water, 33% PC

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	148.4	178.8	0.83

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone	1.15×10^{-7}
	After naltrexone, 10^{-7}M	4.00×10^{-6}
	After UM 979, 10^{-7}M	1.25×10^{-6}

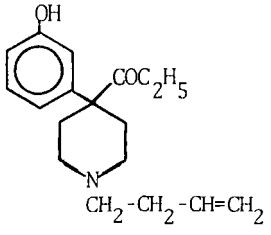
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} (M)	Drug alone	4.12×10^{-7}
	After naltrexone, 10^{-8}M	7.69×10^{-7}
	After UM 979, 10^{-7}M	1.17×10^{-6}

SUMMARY

This compound is not a typical morphine-like agonist. Its potency in binding predicts in vivo activity at doses higher than morphine. The intermediate sodium response ratio is not predictive of the nature of the in vivo activity. In both smooth muscle preparations the compound has agonist activity, which is morphine-like in the guinea pig ileum and unlike morphine in the mouse vas deferens.

UM 1196 NIH 9648



N-3-Butenylnorketobemidone hydrobromide

Doses tested: SDS, 0.2-1.6 mg/kg; normals 3.2 mg/kg.

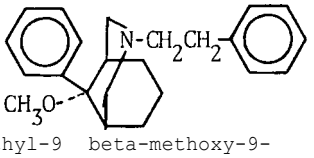
MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.29 (0.21-0.40)

PHYSICAL DEPENDENCE IN MONKEYS

A narcotic agonist, approximately equal to morphine in potency but shorter in duration. The reversal of the drug's effects by nalorphine and naloxone was somewhat atypical, in that apparent recovery was followed by increased CNS depression which lasted for one hour or more.

UM 1199 NIH 9673



3-Phenethyl-9 beta-methoxy-9-phenyl-3-azabicyclo(3.3.1)-nonane hydrochloride

MOUSE ANALGESIA, ED_{50} (mg/kg)

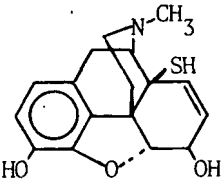
Hot Plate: 0.6 (0.45-0.80)

Nilsen: ---

PHYSICAL DEPENDENCE IN MONKEYS

A narcotic agonist, more potent and and longer lasting than morphine. Doses tested: SDS, 0.04-0.6 mg/kg, Normals, 0.6. Vehicle: water

UM 1202 NIH 9701



SUMMARY

UM 1202 appears to have narcotic agonist actions in these preparations with considerably less potency than morphine.

14 beta-Mercaptomorphine hydrochloride hydrate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	1412	693	2.04

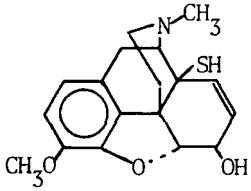
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} approximately 1 x 10^{-5}M. Maximum depression was 60% at 3 x 10^{-5}M. Naltrexone (10^{-7}M) antagonized UM 1202, but EC_{50} not determined because supply of drug was insufficient.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} approximately 1 x 10^{-5}M. Maximum depression was 100% at 1 x 10^{-4}M. Naltrexone (10^{-8}M) antagonized effects of UM 1202.

UM 1203 NIH 9702



SUMMARY

This compound has a low potency in each of the preparations. The results from the smooth muscle preparations suggest a narcotic agonist component of action due to the type of response observed and by the antagonism with naltrexone.

14 beta-Mercaptocodeine

DISPLACEMENT OF STEREO SPECIFIC ^{3}H-ETORPHINE BINDING

The EC_{50} was higher than 15 µM, which is the concentration at which dextrorphan also displaces the ligand.

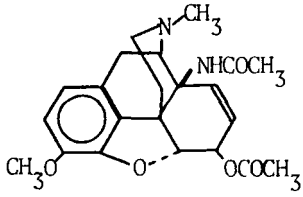
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} approximately 8 x 10^{-5}M. Maximum decrease was 100%. Naltrexone antagonized the actions of UM 1203.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

In doses of 1 x 10^{-5}M to 3 x 10^{-4}M, the drug decreased the twitch to a maximum of 88%. Naltrexone (10^{-8}M) antagonized the action of UM 1203. EC_{50} values were not determined because of the limited supply of drug.

UM 1204 NIH 9703



SUMMARY

It is unlikely that UM 1204 has either narcotic agonist or antagonist properties. Interestingly, it enhances the twitch in the mouse vas deferens preparation.

14 beta-Acetamidocodeine-6-acetate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

The EC_{50} value was higher than 2000 nM.

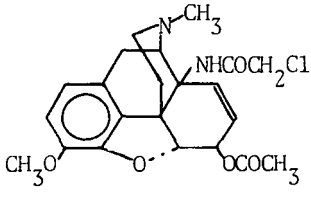
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

Concentrations from 10^{-9} M to 10^{-4} M were tested. The maximum decrease was 18.4% of the control twitch at 3 x 10^{-5} M. Naltrexone, 10^{-7} M, did not alter the response to UM 1204. EC_{50}'s could not be determined and probably would have little significance when the maximum response is so small.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

Concentrations between 3 x 10^{-6} M and 1 x 10^{-4} M increased the magnitude of the twitch. Naltrexone had no effect on this action.

UM 1205 NIH 9704



SUMMARY

This drug does not have typical morphine-like agonist actions in these preparations. Like UM 1204, it enhances the twitch in the electrically driven mouse vas deferens.

14 beta-Chloroacetamidocodeine-6-acetate

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	13800	9970	1.38

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

Concentrations between 10^{-9} M and 10^{-4} M had no effect on the magnitude of the twitch.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVE MOUSE VAS DEFERENS

Concentrations between 10^{-6} M and 10^{-4} M increased the twitch magnitude (5.2 fold at 10^{-4}M). The EC_{50} for this effect was approximately 2 x 10^{-5} M.

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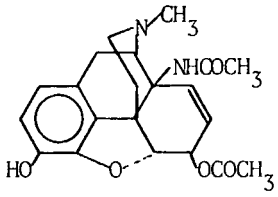
UM 1206 NIH 9705



14 beta-Acetamidomorphine-6-acetate hemihydrate

SUMMARY

The compound is not a morphine-like agonist. It has a very high sodium response ratio and binds with an affinity between those of morphine and propoxyphene. It does not inhibit the twitch in the guinea-pig ileum to the extent that morphine does, and it enhances the twitch in the mouse vas deferens.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	848.8	167.1	5.08

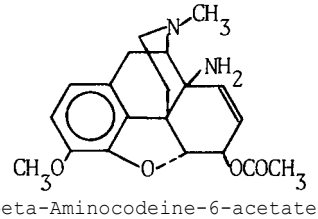
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

UM 1206 decreased the twitch slightly in concentrations between 3 x 10^{-6} M and 10^{-4} M. The maximum decrease was 25.4% and occurred at the the highest concentration studied. Neither naltrexone nor UM 979 affected the action of UM 1206.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

In concentrations between 10^{-6} M and 10^{-4} M it increased markedly the magnitude of the twitch, to a maximum of 20 times the control.

UM 1207 NIH 9706



14 beta-Aminocodeine-6-acetate

SUMMARY

Receptor binding suggests that UM 1207 is a narcotic agonist of low potency. In the guinea-pig ileum and mouse vas deferens preparations, the pattern of effects produced by the narcotic antagonists suggests atypical agonist activity.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	5780	3500	1.65

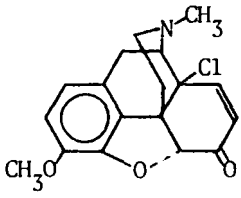
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone (maximum depression 78.9%)	1.15 x 10^{-9}
	After naltrexone, 10^{-7} M	1.28 x 10^{-9}
	After UM 979, 10^{-7}M	1.65 x 10^{-8}

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} (M)	Drug alone (maximum depression 37.5%)	2.41 x 10^{-9}
	After naltrexone, 10^{-8} M	2.03 x 10^{-9}
	After UM 979, 10^{-8} M	4.87 x 10^{-9}

UM 1208 NIH 9707



14 beta-Chlorocodeinone

SUMMARY

This drug is not a morphine-like agonist. The transient increases in magnitude of the twitch in the mouse vas deferens are most unusual.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

The EC_{50} was higher than 15000 nM, which is the value of dextrorphan in displacing etorphine.

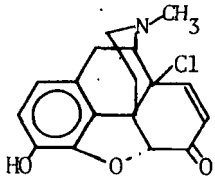
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

The dose-response curve was biphasic. The initial decreases occurred over the range of 3 x 10^{-10} M to 10^{-7} M and were completely abolished by naltrexone, 10^{-7} M and UM 979, 10^{-7} M. The second phase occurred over a range of 3 x 10^{-7} M to 10^{-6} M and was not affected by either antagonist.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

At lower concentrations (10^{-9} M to 10^{-5} M), it caused slight decreases in twitch which were not affected by naltrexone, 10^{-8}M or UM 979, 10^{-8} M. At 10^{-5} M and higher concentrations, the drug caused large, but very transient increases in the size of twitch.

UM 1209 NIH 9708



14 beta-Chloromorphinone

SUMMARY

In all three preparations, UM 1209 is a narcotic agonist, less potent than morphine. It is antagonized by naltrexone but not by UM 979, suggesting that it is a "mu" agonist.

DISPLANCEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	434	317	1.37

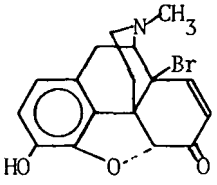
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone (maximum depression 36.7%)	1.12 x 10^{-6}
	After naltrexone, 10^{-7} M	2.00 x 10^{-4}
	After UM 979, 10^{-7} M	1.75 x 10^{-6}

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} (M)	Drug alone (maximum depression 85.2%)	1.04×10^{-6}
	After naltrexone, 10^{-8} M	8.43×10^{-6}
	After UM 979, 10^{-8} M	1.44×10^{-6}

UM 1210 NIH 9709



SUMMARY

UM 1210 behaved like a morphine-type agonist in all three preparations.

14 beta-Bromomorphinone

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	759	460	1.65

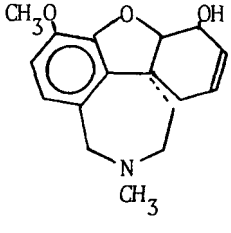
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone (maximum depression 48.5%)	2.67×10^{-6}
	After naltrexone, 10^{-7} M	3.63×10^{-5}
	After UM 979, 10^{-7} M	9.77×10^{-6}

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} (M)	Drug alone [maximum depression 89.4%)	8.24×10^{-7}
	After naltrexone, 10^{-8} M	1.97×10^{-5}
	After UM 979, 10^{-8} M	2.79×10^{-6}

UM 1211 & 136 NIH 9712 & 7380



SUMMARY

This drug was without effects in these three preparations.

(-)-Galanthamine hydrobromide

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

EC_{50} was greater than 20000 nM.

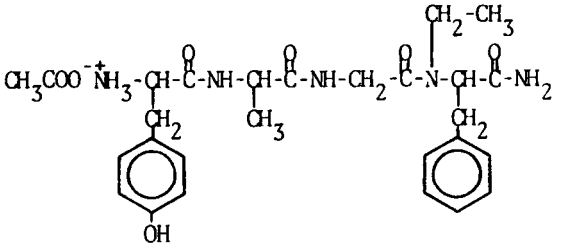
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA PIG ILEUM

No depression in doses between 10^{-9} M and 10^{-4} M.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

No depression in doses between 10^{-9} M and 10^{-4} M.

UM 1213 NIH 9725 MCV 4188



L-Tyrosyl-D-alanylglycyl-L-N-alpha ethylphenylalanine amide acetate

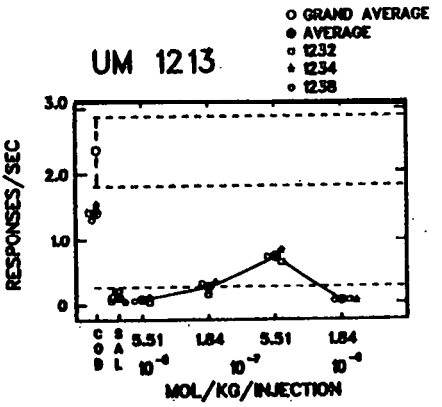
MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.73 (0.59-0.90) Nilsen: ---

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This is a morphine-like narcotic agonist with a very flat dose-response curve. Doses tested: SDS, 0.5-16 mg/kg. Vehicle: water

SELF-ADMINISTRATION BY MONKEYS



UM 1213 maintained drug self-injection responding at rates above those of saline but only at 52 per cent of the maximum rate of codeine self-injection (0.3 mg/kg/injection). The dose that maintained the maximum rates of responding was 5.5×10^{-7} mol/kg/injection (0.3 mg/kg/injection); higher and lower doses were less effective.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	8.17	4.92	1.66

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M) Drug alone (maximum depression 27.3%)	1.01×10^{-8}
After naltrexone, 10^{-7} M	7.72×10^{-8}
After UM 979, 10^{-7}	1.41×10^{-8}

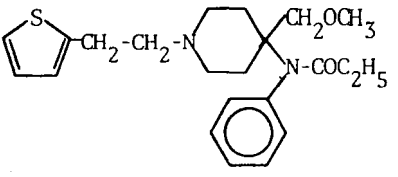
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} (M)	Drug alone (maximum depression 98.3%)	1.09×10^{-8}
	After naltrexone, 10^{-8} M	1.42×10^{-7}
	After UM 979, 10^{-8} M	7.10×10^{-8}

SUMMARY

UM 1213 appears to be a morphine-like agonist in all of our preparations. The drug is equal to or more potent than morphine on the in vitro preparations but less potent than morphine on the in vivo preparations.

UM 1214 NIH 9726 MCV 4191 Sufentanil citrate



MOUSE ANALGESIA, EC_{50} (mg/kg)

Hot Plate: 0.004 (0.003-0.005)

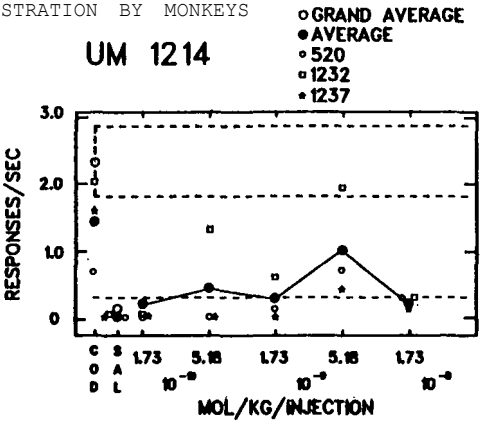
Nilsen: ---

N-(4-(Methoxymethyl)-1-(2-(2-thienyl)ethyl)-4-piperidinyl)-N-phenylpropanamide 2-hydroxy-1,2,3-propane-tricarboxylate (1:1)

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This is a very potent, short-acting narcotic agonist. Doses tested: SDS, 0.0005-0.004 mg/kg. Vehicle: water.

SELF-ADMINISTRATION BY MONKEYS



UM 1214 maintained self-injection responding at rates comparable to codeine in two of three monkeys at a dose of 5.2×10^{-9} mol/kg/injection. In the third monkey, maximum rates were maintained at the same dose, but the rates were lower than codeine. UM 1214 at the two highest doses studied suppressed codeine self-injection for a number of sessions after these doses were substituted. This phenomenon has not been observed previously with other drugs that have high potency (e.g., etorphine, fentanyl).

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	7.79	4.15	1.87

NOTE: In the absence of Na^{+}, the drug exhibited a biphasic pattern in inhibiting ^{3}H-etorphine binding. The cross-over point of the two linear portions of the log-probit plot occurred at the EC_{50} value, which was 4.15 nM. The biphasic response represents a unusual phenomenon hitherto not encountered in displacing opiate receptor binding of ^{3}H-etorphine by various narcotic drugs.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone	5.9×10^{-16}
	After naltrexone, 10^{-7}M	5.0×10^{-12}
	After UM 979, 10^{-7} M	3.9×10^{-12}

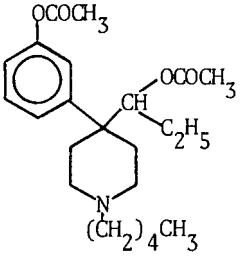
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} (M)	Drug alone	4.4×10^{-9}
	After naltrexone, 10^{-8} M	9.2×10^{-8}
	After UM 979, 10^{-8} M	1.3×10^{-8}

SUMMARY

UM 1214 resembles morphine in each of the preparations in which it was studied. Its sodium ratio is similar to that of narcotic agonists. It suppresses electrically induced twitches in both smooth muscle preparations and it is reversed by both narcotic antagonists in these preparations. It suppresses narcotic withdrawal in morphine-dependent Rhesus monkeys. It supports drug self-injection in these monkeys.

UM 1215 NIH 9729 MCV 4193



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.49 (0.34-0.72)

Nilsen: ---

4-(m-Acetoxyphenyl)-4-(1-acetoxypropyl)-1- n -pentylpiperidine oxaiate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

In the doses tested, UM 1215 neither precipitated nor suppressed the signs of morphine abstinence, nor did it modify the monkeys' behavior in any other detectable way. Doses tested: SDS, 0.3-4.8 mg/kg; NW, 0.3, 0.6 mg/kg. Vehicle: water, 25% propylene glycol, heat

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	351.8	154.3	2.28

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone (maximum depression 63%)	2.14×10^{-8}
	After naltrexone, 10^{-7} M	1.84×10^{-5}
	After UM 979, 10^{-7} M	2.48×10^{-6}

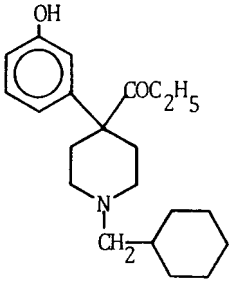
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

EC_{50} was 4.07×10^{-8} M. Maximum depression was 50 per cent. Neither naltrexone (10^{-8} M) nor UM 979 (10^{-8} M) antagonized the actions of UM 1215.

SUMMARY

Results from receptor binding and guinea pig ileum suggest a morphine-like component of action for this drug. The inhibitory actions on the mouse vas deferens are different in mechanism in that there is only a half-maximal suppression of the twitch and that is refractory to narcotic antagonism. These data, taken together with the information from the morphine-dependent monkey, are interesting because UM 1215 was without effect in suppressing the signs of morphine abstinence in doses that, on the basis of the binding and guinea-pig-ileum data, would be expected to be effective.

UM 1218 NIH 9585



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: No dose response

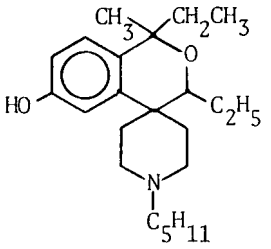
Nilsen: ---

N-Cyclohexylmethylnorketobemidone hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

In the doses tested, this drug had no apparent effect upon the behavior of the monkeys. The supply of drug was depleted so that higher doses could not be evaluated. Doses tested: SDS, 5.0-10 mg/kg. Vehicle: water, 33% propylene glycol, heat

UM 1219 NIH 9734 MCV 4194



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: Inactive to 100 mg/kg

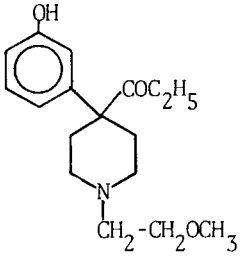
Nilsen: ---

dl-Spiro ((1,3-diethyl-1-methyl-7-hydroxy-1H-2-benzopyran)-4,4'-(1-pentylpiperidine)) hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

At the doses tested, UM 1219 neither suppressed nor precipitated the signs of morphine abstinence. Drug supply was depleted, so higher doses were not tested. Doses tested: SDS, 5.0-20 mg/kg
Vehicle: ethanol + Emulphor

UM 1220 NIH 9740 MCV 4201



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 0.73 (0.55-0.98)

Nilsen: 2.1 (1.4-3.1)

N-(2-Methoxyethyl)-norketobemidone oxalate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This compound is a short-acting narcotic agonist, somewhat more potent than morphine. Doses tested: SDS, 0.06-0.5 mg/kg., Normals, 0.5 mg/kg, Vehicle: water

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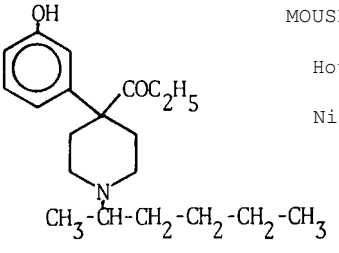
UM 1221 NIH 9741



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: No dose response

Nilsen: ---

N-2-Hexylnorketobemidone hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

In the doses tested, this drug had no obvious effect upon the behavior of the animals. Drug supply was depleted so that higher doses could not be tested. Doses tested: 5.0-20 mg/kg. Vehicle: 50% ethanol + 50% water

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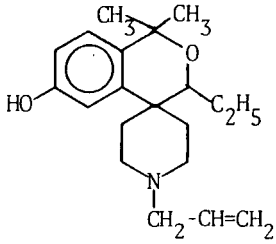
UM 1222 NIH 9742



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: Insufficiently active for assay

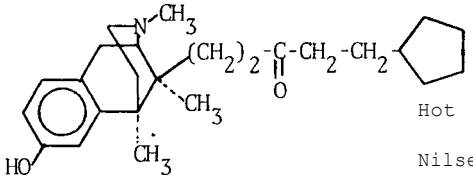
Nilsen: Inactive to 50 mg/kg

Spiro((1,1-Dimethyl-3-ethyl-7-hydroxy-1H-2-benzopyran)-4,4'-(1-allylpiperidine)) hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This drug neither suppressed nor precipitated abstinence signs in the doses which were tested. Doses tested: SDS, 5.0-10 mg/kg. Vehicle: 50% ethanol + 50% water, heat.

UM 1228 NIH 9751 MCV 4202



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: No dose response

Nilsen: Inactive to 100 mg/kg

(2 alpha, 6 alpha, 11S)-(+)-1-Cyclopentyl-5-(1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-y1)-3-pentanone methanesulfonate.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	290.4	471.2	0.62

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

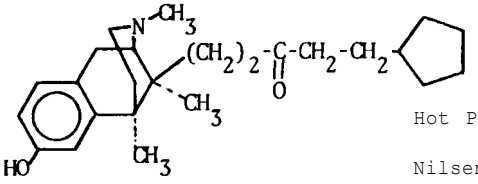
UM 1228 suppressed the twitch at 10^{-5} M and this effect was not prevented by naltrexone (10^{-7} M). The drug had no effect upon responses to morphine when administered in concentrations up to 10^{-6} M, 15 minutes before determining the morphine concentration-effect curve.

SUMMARY

This is the essentially inactive dextro isomer of UM 1229.

1229 NIH 9752 MCV 4203

MOUSE ANALGESIA, ED_{50} (mg/kg)



Hot Plate: No dose response

Nilsen: Inactive to 100 mg/kg

(2 alpha, 6 alpha, 11S)-(-)-1-Cyclopentyl-5-(1,2,3,4,5,6-hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl)-3-pentanone methanesulfonate

DISPLACEMENT OF STEROSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	1.78	2.22	0.80

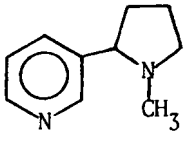
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

UM 1229 produced an unsurmountable (noncompetitive) inhibition of the response to morphine when administered in concentrations as low as 10^{-12} M. The drug inhibits the electrically induced twitch at 10^{-5} M, and this effect is not prevented by naltrexone (10^{-7} M).

SUMMARY

This drug, the active levo isomer of UM 1228, is a potent opioid antagonist, comparable to or more potent than naltrexone. The unsurmountable nature of the interaction of UM 1229 with morphine in the guinea-pig ileum preparation suggests that the compound may have a long duration of action.

UM 1230 NIH 9733 MCV 4194



MOUSE ANALGESIA, EC_{50} (mg/kg)

Hot Plate: 2.2 (1.6-3.0)

Nilsen: 19.6 (13.6-28.1)

(-)-Nicotine di-l-tartrate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

At the doses tested, this drug neither suppressed nor precipitated the signs of morphine abstinence. Doses tested: SDS, 0.5-4.0 mg/kg Vehicle: water

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

UM 1230 has an EC_{50} greater than 2000 nM.

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

No effect over the range from 10^{-9} M to 10^{-4} M.

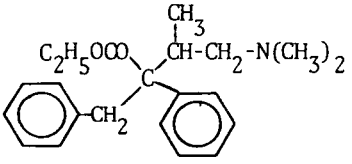
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

No effect over the range from 10^{-9} M to 10^{-4} M.

SUMMARY

This compound was inactive in all of the tests performed.

UM 1231 NIH 9757 MCV 4204



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 3.8 (2.8-5.2)

Nilsen: 7.1 (5.3-9.4)

dextro-Propoxyphene hydrochloride

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

A narcotic agonist which is less potent than morphine. Doses tested: SDS, 2.0-16 mg/kg. Normals, 12-16 mg/kg. Vehicle: water

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	10175	1795	5.67

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA PIG ILEUM

EC_{50} (M) Drug alone (maximum depression 92.4%)	5.45×10^{-6}
After naltrexone, 10^{-7} M	7.62×10^{-6}
After UM 979, 10^{-7} M	7.32×10^{-6}

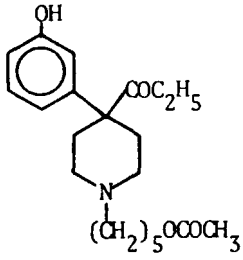
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

UM 1231 increased the magnitude of the twitch to a maximum of 2.4 fold at a drug concentration of 3×10^{-5} M. In the presence of naltrexone, 10^{-8} M, caused a greater enhancement to a maximum of 5.6 fold. UM 979, 10^{-8} M, did not alter the response to UM 1231.

SUMMARY

UM 1231 suppressed the withdrawal syndrome in the monkey with a potency 1/5 that of morphine. In the in vitro preparations, it was considerably less potent than morphine and had unusual properties. In the binding assay it had a very large sodium response ratio. On the mouse vas deferens, it produced enhancement which was potentiated by naltrexone. Thus, while appearing to be a morphine-like compound in the dependent monkey, UM 1231 has a variety of non-morphine-like actions in the other preparations.

UM 1232 NIH 9769



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 23.6 (17.7-31.5)

Nilsen: ---

N-Pentylacetate norketobemidone

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

At the doses tested, this compound had very little pharmacological effect. At the highest dose, there was a slight suggestion of antagonist activity, but the supply of drug was depleted and higher doses could not be tested. Doses tested: SDS, 5.0-20 mg/kg. Vehicle: 50% ethanol - 50% water, heated to put into solution.

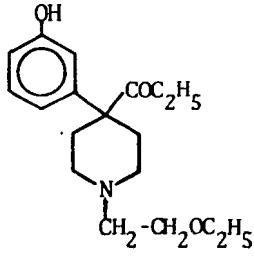
DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	1957	2200	0.89

SUMMARY

UM 1232 appears to be a narcotic antagonist of very low potency.

UM 1233 NIH 9770



MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 1.8 (1.4-2.2)

Nilsen: ---

N-(2-Ethoxyethyl) norketobemidone oxalate

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

A narcotic agonist, approximately equal to morphine in potency and duration of action. Doses tested, 0.8-6.4 mg/kg. Vehicle: 50% ethanol-50% water, heated to put into solution.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	1061	643	1.65

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA-PIG ILEUM

EC_{50} (M)	Drug alone (maximum depression 38.6%)	2.63×10^{-6}
	After naltrexone, 10^{-7} M	3.27×10^{-5}
	After UM 979, 10^{-7} M	1.11×10^{-5}

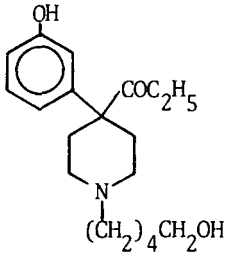
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

The responses of the mouse vas deferens to UM 1233 are complex. At concentrations between 10^{-7} M and 10^{-5} M, the drug slightly suppressed the twitch. At higher concentrations the magnitude of the twitch increased greatly. UM 979, 10^{-8} M, had no effect on the responses to UM 1233. However, naltrexone, 10^{-8} M, completely antagonized the suppression of the twitch by UM 1233 and consequently enhanced the increases in twitch magnitude produced by higher concentrations.

SUMMARY

UM 1233 is morphine-like in the withdrawn Rhesus monkey. In displacing etorphine, it is only 1/10 as potent as morphine. This type of disparity is infrequent but has been seen with meperidine-like drugs in the past. In the guinea-pig ileum, the compound was considerably less potent than morphine. The morphine-like actions of UM 1233 upon the mouse vas deferens are obscured by the increases in twitch magnitude which are produced by this drug.

UM 1237 NIH 9789



MOUSE ANALGESIA, EC_{50} (mg/kg)

Hot Plate: Inactive

Nilsen: ---

5-Hydroxypentyl norketobemidone hydrobromide

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

The compound neither suppressed nor precipitated the signs of morphine abstinence. Doses tested: 5.0-10 mg/kg. Vehicle: water

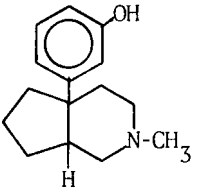
DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	1236	802	1.54

SUMMARY

If this is a narcotic agonist, it is a weak one.

UM 1242 NIH 9576 MCV 4157



MOUSE ANALGESIA, EC_{50} (mg/kg)

Hot Plate: 2.4 (1.6-3.7)

Nilsen: ---

cis-(-)-3-(Octahydro-2-methyl-1H-1-2-pyridin-4a-yl)phenol, (Z)-2-butenedioic acid salt

PHYSICAL DEPENDENCE EVALUATION IN RHESUS MONKEYS

This drug had no effect upon the progression of abstinence signs in morphine-dependent monkeys. Doses tested: SDS, 4.0-32 mg/kg. Vehicle: water.

DISPLACEMENT OF STEREOSPECIFIC ^{3}H-ETORPHINE BINDING

	+Na	-Na	+Na/-Na
EC_{50} (nM)	1077	497	2.17

DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN GUINEA PIG ILEUM

Concentrations between 10^{-6} M and 3 x 10^{-4} M increased the magnitude of the twitch and also increased the baseline tension. Neither naltrexone, 10^{-7} M, nor UM 979, 10^{-7} M altered the response to UM 1242.

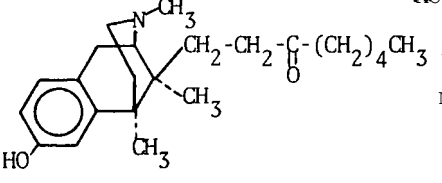
DEPRESSION OF TWITCH IN ELECTRICALLY DRIVEN MOUSE VAS DEFERENS

This drug had no consistent effect upon the vas deferens preparation.

SUMMARY

UM 1242 appears to be devoid of narcotic activity at the doses tested in the withdrawn monkeys; it also shows no narcotic agonist activity on the smooth muscle preparations. In the binding assay, it is approximately 1/10 as potent as morphine and has an agonist-like sodium response ratio.

UM 1258 NIH 9624 MCV 4175

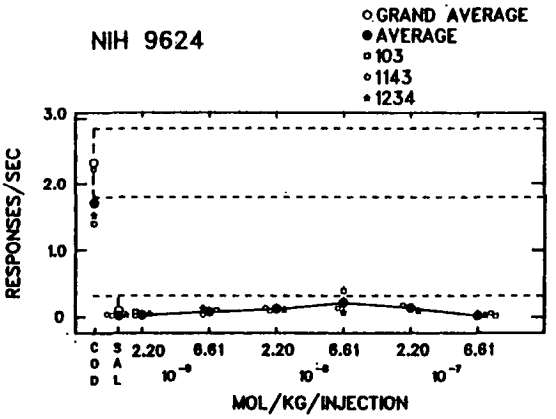


MOUSE ANALGESIA, ED_{50} (mg/kg)

Hot Plate: 2.4 (1.7-3.3)

Nilsen: ---

1-((2 alpha, 6 alpha, 11S)-dl-1-(1,2,3,4,5,6-Hexahydro-8-hydroxy-3,6,11-trimethyl-2,6-methano-3-benzazocin-11-yl))-3-octanone methanesulfonate



No injection dose of UM 1258 maintained rates of self-injection behavior higher than those maintained by saline.

ACKNOWLEDGMENT. The authors wish to acknowledge the excellent technical assistance of Fred M. Adams, Patricia J. Dahlstrom, Janet Fekete, James E. Goodrich, Lee L. Labadie and Kathi Watson.

This work was supported by Grant DA 00254-08 from the National Institute on Drug Abuse and by The Committee on Problems of Drug Dependence, Inc.

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Dopamine and Serum Prolactin in Methadone Withdrawal

M. S. Gold, A. L. C. Pottash, I. Extein, and H. D. Kleber

We have hypothesized that chronic exogenous opiate administration might cause a decrease in endogenous opiate release and synthesis as well as a decrease in opiate receptor sensitivity (1-4). Abrupt discontinuation of chronic opiate administration would, according to our model system, result in the absenceof exogenous opiate-mediated inhibition of ascending norepinephrine (NE) activity. As a result of this release from chronic exogenous inhibition and the absence of adequate inhibitory neurotransmitters at the level of the NE nucleus (4), there would be a resultant large increase in NE activity, release, and turnover (1,5). Attempts to use endorphin stores to autoregulate this profound locus coeruleus (LC) firing increase would be too little too late, as the stores of available endogenous opiates would be of insufficient quantity and the receptor sensitivity would be too low to augment the available m-Enkephalin. In addition, it is likely that other available inhibitory presynaptic neuro transmitters such as epinephrine (E) and NE would be of insufficient quantity and interact with receptors which are themselves abnormal to reverse the NE "rebound" release from opiate mediated inhibition (4).

We tested the efficacy of clonidine in opiate withdrawal not only to demonstrate that clonidine might be a new and important treatment for addicts (6) but also to see which physiological and affective variables would be clonidine-reversible and thereby attributable to clonidine's agonistic effects on presynaptic alpha-2 receptors on the LC. We had speculated that clonidine would reverse in man the behaviors and affective state produced by electrical or pharmacological activation of the IC as we had demonstrated in primates. Our LC or NE hyperactivity hypothesis was supported by knowledge of LC neuroanatomy. The known anatomical connections of the LC suggested an important role for this structure in the wide variety of behaviors and physiological changes which accompany drug-withdrawal and spontaneous panic states. The LC also receives afferents from serotonergic, adrenergic, peptidergic and noradrenergic neurons, the hypothalamus, and may have transducer cells to receive and relay hormonal messages (4,7,8). This LC neuroanatomy supports an

important neuromodulatory or "tone" role for the LC and does not necessitate the direct involvement of numerous brain systems in the feeling state, cardiovascular, sympathetic, parasympathetic, and many other manifestations of opiate withdrawal states (1,4).

After we administered 5 ug/kg of clonidine and placebo double-blind, orally in matching vehicles to 5 male opiate (methadone) addicts (1) we recognized that clonidine was effective for the full spectrum of withdrawal signs, symptoms and affects. All of our clinical data on the antiwithdrawal efficacy of clonidine in man (1-6) served to offer strong support for an important Endorphin-LC interaction and NE hyperactivity as the most critical event in the generation of withdrawal symptom on the basis of clonidine's known effects on the LC and NE activity when given in low doses. This NE hypothesis could only be directly investigated in animal studies. In rodent and primate studies it was demonstrated that clonidine decreased NE activity, release and turnover as assessed by changes in the brain's major NE metabolic MHPG (4,9-11). Morphine and endogenous opiates were found to have a similar effect through interaction with LC opiate receptors as assessed by naloxone reversal (12,13). Finally, Aghajanian (14) demonstrated that chronic exogenous opiate administration produced tolerance of LC neurons to suppression. He also demonstrated that tolerance develops in the LC inhibition response to chronic opiates (in opiate addiction) and that naloxon-precipitated withdrawal was accompanied the predicted noradrenergic hyperactivity. He demonstrated in single neuronal electrophysiological and microiontophoresis studies that this NE hyperactivity could be reversed by clonidine (14). This study confirmed the hypothesized LC hyperactivity (1,4) in withdrawal and supported our notion that NE was the important neurotransmitter in the generation of withdrawal symptoms. Our studies and the studies in the literature (15) did not exclude an important or at least significant role for other brain monoamine nuclei and neurotransmitters in opiate withdrawal. However, we did hypothesize that the NE hyperactivity could be demonstrated directly in studies of animals and man and that this hyperactivity was related to the signs and symptoms of withdrawal (1,2).

This noradrenergic hypothesis can also explain the efficacy of clonidine and other nonopiate treatments for opiate withdrawal (4). However, a dopaminergic hyperactivity hypothesis has also been proposed and supported by a large number of animal studies. This dopamine hypothesis is also supported by a rodent study and a pilot study in humans (16-19) reporting that opiate withdrawal is associated with decreases in serum prolactin (PRL).

Serum PRL is predominantly controlled in vivo and in vitro by an inhibitory dopamimergic mechanism (20,21). Consistent with this control mechanism, augmentation of dopamine activity results in a decrease in serum PRL, whereas inhibitionof dopamine function results in significant increases in serum PRL (20,21). Exogenous and endogenous opiates produce increases in serum PRL (20,21) while opiate antagonists produce decreases in serum PRL in some species and some human studies (20,21).

To evaluate the dopamine hyperactivity hypothesis in man and confirm the pilot data on decreased serum PRL in opiate withdrawal, we measured serum PRL during significant opiate withdrawal in 21 male opiate addicts and after clonidine suppression of opiate withdrawal signs and symptoms. We also measured serum PRL in these addicts 4 weeks after they were free of clonidine and opiates.

METHODS

The subjects were 21 male opiate addicts who had been maintained on 15-80 mg of methadone for more than 6 months. All gave informed consent to participate in a study that involved abrupt discontinuation of methadone and administration of 6 ug/kg of clonidine after at least 36 hours of total abstinence. A research nurse specialist observed and rated the patients as described previously (11) with the subjects at bed rest after an indwelling venous catheter had been in place for 60 minutes. Ratings were done simultaneously with blood samples taken 60 minutes before clonidine administration, at the time of clonidine administration. PRL levels were not measured while the patients were taking methadone because of the known stimulatory effects of methadone on serum PRL (20,21). Subjects had venipuncture performad 4 weeks after clonidine discontinuation for determination of an opiate-free PRL baseline. Urine toxicology was performed weekly by T.L.C. to determine whether patients were drug-free. All samples were placed on ice and centrifuged within 1 hour. Serum was frozen at -20°C until radioimmnoassays were performed in duplicate (20,21).

RESULTS

Clonidine caused a significant decrease in nurse-rated opiate withdrawal signs and symptoms. Opiate withdrawal symptoms decreased from a mean (±SD) just before clonidine administration of 13.8 ± 6.9 to 1.8 ± 2.7 at 60 minutes after clonidine administration and to 0.7 ± 1.8 at 120 minutes after clonidine administration (paired t test; $P<0.01$). Serum PRL was significantly decreased from a mean during peak opiate withdrawal before clonidine (36-72 hours of total abstinence) of 5.3 ± 3.2 as compared to a drug-free baseline of 14.1 ± 2.7. There were no significant changes or effects of clonidine demonstrated as differences between the 0 and 120-minute serum PRL levels. Serum PRL was 4.7 ± 3.3 at 60 and 4.3 ± 3.8 at 120 minutes (paired t, NS).

DISCUSSION

Significant decreases in serum PRL are normally attributable to the administration of drugs or medications which stimulate dopamine receptors or augment dopamine release or neurotransmission, but other neurotransmitters may also inhibit PRL release (20). The decreased serum PRL reported here for patients in significant opiate withdrawal is in agreemant with our previous pilot study (19) and the rodent study of Lal et al. (17). These data support the proposed dopaminergic hyperactivity in opiate withdrawal (16,17,22). However, although the signs and symptoms of opiate withdrawal were reversed by

clonidine, the serum PRL did not return to the normal range or post-addiction levels. This suggests that the dopaminergic hyperactivity my continue for a prolonged period of time irrespective of the symptoms or signs reported or observed. Further studies are necessary with PRL samples taken throughout opiate withdrawal to evaluate this hypothesis.

Clonidine in the doses used in this study is not known to stimulate DA receptors or augment DA turnover. However, it is possible that clonidine may prolong the decrease in serum PRL that accompanies withdrawal through non-DA mechanisms (19).

On the basis of rodent and primate studies and the efficacy of low doses of the presynaptic α-2 agonist clonidine in withdrawal, we have suggested that opiate withdrawal results from increased neuronal activity in noradrenergic areas of the brain that are regulated by α-2 and opiate receptors (1-4). We further suggested that LC might have a rebound release from tonic exogenous opiate-mediated inhibition and that clonidine reverses noradrenergic hyperactivity by replacing opiate with α-2 mediated inhibition of the LC (1-6). Direct electrophysiological (14) and neurochemical (11) investigations in rodents have supported noradrenergic hyperactivity in withdrawal and its relationship to the efficacy of clonidine. Our preliminary studies of plasma levels of 3-methoxy-4-hydroxy-phenethylene-glycol in acute withdrawal and after clonidine in man suggest that noradrenergic hyperactivity is present, and may be related to the symtoms of withdrawal the efficacy of clonidine in withdrawal. Other neurotransmitter and neural peptides systems also be involved in the data reported here and elsewhere.

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The Generality of Benefits From Alcohol and Drug Abuse Treatments

A. T. McLellan, L. Luborsky, G. E. Woody, and C. P. O'Brien

INTRODUCTION

As part of a large treatment evaluation study (McLellan et al. 1980) we collected data on the severity of chemical use, as well as five other problem areas, from samples of alcoholics and drug addicts at admission to treatment and at follow-up six months later. These data provided a natural opportunity: (1) To examine the relationships between the severity of alcohol/drug use and the status of the other problem areas prior to and following treatment; (2) To determine if improvement in alcohol/drug use was related to improvement in the other problem areas.

METHOD

Subjects - Subjects were drawn from the 1035 male, service veterans who were admitted to alcohol (n=671) or drug abuse (n=364) rehabilitation programs at the Coatesville or Philadelphia VA Hospitals during 1978. We excluded patients who dropped out of treatment prior to 5 inpatient days or 5 outpatient visits. We were able to follow up approximately 85 percent of the remaining 879 patients six months after admission to treatment, and complete data was therefore available on 460 alcoholic and 282 drug addicted clients (total n=742).

Data Collection

The admission and follow-up evaluations were based upon data from the Addiction Severity Index (ASI) (McLellan et al. 1980). The ASI is a structured 30-40 minute, clinical research interview designed to assess problem severity in six areas commonly affected by addiction: medical, legal, substance abuse, employment, family, and psychological function.

In order to develop valid general measures of outcome in each of the problem areas, and to overcome the inherent unreliability of single-item criteria (Nunnally 1967), we constructed criterion composites from sets of single items within each of the ASI problem areas.

Several items from each problem area were intercorrelated to exclude those which were unrelated. The remaining items were standardized and tested for conjoint reliability using Cronbach's formula (Cronbath 1970). A set of 4 to 6 items from each area was selected using this procedure, and each set showed a standardized reliability coefficient of .73 or higher. Seven composites [medical problems, employment, drug use, alcohol use, legal status, family problems, and psychological function) were constructed in this manner, and scores on each composite were calculated for all patients at admission and follow-up, with higher scores indicating greater problem severity.

RESULTS

Pre-Treatment Problem Status Correlations - Pearson product-moment correlations were calculated among the seven retreatment problem status composites as a means of determining the nature and extent of the relationships among them. The results are presented for the total population in the top portion of table 1. As can be seen, the coefficients were generally quite low, including the relationships between alcohol/drug use with the other problem areas. Although four coefficients were large enough to be statistically significant ($p < .01$) this was more a function of the population size than the strength of the relationships, since even the largest coefficient (.44) accounted for less than 19% of joint variation.

The significant negative correlations between alcohol use and drug use, and between alcohol use and legal status, reflected the essential differences between the Alcoholic and Drug Addict samples within our population. To test the possibility that extreme variation between these samples was masking more robust relationships within each group, we calculated the correlations separately, and these results are presented in the lower portion of table 1. While the separation of these samples did expose some differences, in general the correlations remained low in both groups. The few significant relationships were common to both samples and were not surprising. For example, the severity of drug use was directly related to the severity of the legal problem, and the severity of the family problem was directly related to the severity of the psychological problem.

These findings confirm our previous reports (McLellan et al. 1980) with another set of measurements, and indicate the independence of the separate problem areas and the lack of a general relationship between the chemical abuse measures and the remaining problem areas in this population at the time of admission.

Post-Treatment Problem Status Correlations

Although the correlations between the pretreatment measures were generally low, it remained possible that the posttreatment status of the problem areas would be generally related to the outcome status of the chemical abuse problems. As a test of this possibility, we again intercorrelated the problem status measures for the entire

population and for the alcoholic and drug addict samples at the time of followup. Again, generally low correlations were shown for the total population and for the individual samples. Although more significant relationships were seen in the followup data than were seen in the pretreatment results, the magnitude of the relationships remained low, and there did not appear to be a tendency toward a general relationship between the chemical abuse measures and the remaining problem areas. However, there was an indication of a general relationship between the psychological problem status and most of the other problem areas in the total population and in each of the samples.

Correlation Among Improvement Scores

As a test of the generality of treatment effects, we calculated residual change scores (which equated individuals for different pretreatment scores) on each of the criterion measures and then intercorrelated these residualized change measures. If treatment for drug and alcohol abuse produced general effects, then there should be generally significant relationships among the change scores, especially between the change in chemical abuse and the other scores. The results of these intercorrelations are presented for the total population in the top portion of table 2, and again the correlations were strikingly low, especially between the chemical abuse change scores and change in the other problem areas. As in the case of the Posttreatment Status results, there appeared to be a clear, if not large, relationship between change in psychological status and change in the other areas.

When these intercorrelations were examined separately for the two samples (lower portion, table 2), similar results were obtained. Most correlations were quite low for both samples, yet four significant relationships were seen in each sample between the psychological change score and the other change measures. Again, no general relationships were seen between change in drug use and change in the other areas.

SUMMARY AND DISCUSSION

We tested the relationships between severity of chemical abuse and the status of several other problems commonly associated with addiction, by intercorrelating highly reliable problem status measures in samples of male alcoholics and drug addicts before and after substance abuse treatment. The results for the total population and for each of the samples showed very low correlations generally, and virtually no evidence of a general relationship between the chemical abuse measures and the remaining problem areas. We then tested the generality of treatment effects by calculating residual change scores on each of the problem measures and intercorrelating these scores. Again, the correlations were quite low with no suggestion of a general relationship between improvement in the chemical abuse problem and improvement in the other areas. While no general relationships were found between chemical abuse and the other problem areas, the posttreatment psychological status was

TABLE 1

PRETREATMENT CORRELATIONS OF PROBLEM STATUS MEASURES
TOTAL POPULATION (N=742)

	EMPLOY	ALCOHOL	DRUG	LEGAL	FAMILY	PSYCH
MED	.09	.11	.07	-.06	.07	.12
EMP		.08	.04	.03	.05	.14
ALC			-.22*	-.24*	.11	.09
DRG				.44*	.14	.08
LEG					.09	.05
FAM						.34*

ALCOHOLICS (N=460) 9

	EMP	ALC	DRG	LEG	FAN	PSY
MED	.11	.15	.01	.00	.07	.10
EMP		.17*	.03	.00	.02	.10
ALC			-.09	-.01	.11	.07
DRG				.73*	.12	.04
LEG					.04	.15
FAM						.33*

DRUG ADDICTS (N=282) 10

	EMP	ALC	DRG	LEG	FAM	PSY
MED	.05	.08	.07	-.09	.10	.18
EMP		.08	.05	.02	.11	.22
ALC			-.07	-.02	.08	.18
DRG				.32*	.18	.08
LEG					.07	.05
FAM						.36*

* = p< .01

TABLE 2

CORRELATION OF RESIDUALIZED CHANGE SCORES OK PROBLEM STATUS MEASURES
TOTAL POPULATION (N=742)

	EMPLOY	ALCOHOL	DRUG	LEGAL	FAMILY	PSYCH
MED	.05	.14*	.02	.02	.07	.19*
EMP		.03	.04	.11	.13	.09
ALC			.08	.02	.15*	.22*
DRG				.19*	.08	.23*
LEG					.10	.15*
FAM						

ALCHOHOLICS (N=460)

	EMP	ALC	DRC	LEG	FAM	PSY
MED	.06	.07	.04	.02	.07	.23*
EMP		.16*	-.03	-.06	.09	.19*
ALC			.04	.03	.21*	.21*
DRG				.13	.02	-.01
LEG					.01	.11
FAM						.29*

DRUG ADDICTS (N=282)

	EMP	ALC	DRG	LEG	FAM	PSY
MED	.04	-.05	-.03	-.05	.10	.24*
EMP		-.01	.01	.15	.20*	.09
ALC			-.09	-.08	.08	.19*
DRG				.21*	.09	.17*
LEG					.06	.16
FAM						.31*

* = p < .01

generally related at a moderate level to the posttreatment status of the other measures, and psychological improvement was generally related to improvement in most of the other problem areas.

Generality of Treatment Benefits

The low intercorrelations among the problem status measures at followup and among the residual change scores were surprising in light of the many evaluation studies (Armor et al. 1976; Pattison 1976; Simpson et al. 1978) which have shown general population improvements in the areas of legal status, employment, and social relationships following alcohol and drug abuse treatments. However, the general improvements reported in these evaluation studies are a function of population averages compared before and after treatment. This does not mean that most patients presented with most problems and that most improved. McLellan et al. have pointed out how subgroups of patients within a population may show different patterns of treatment problems, and extremely different patterns of change. These different groups are not recognized when only population statistics are reported.

Despite the low intercorrelations demonstrated between the improvement scores, it would be rash to dismiss the potential importance of improvement in the substance abuse problem for the long term maintenance of treatment benefits. The followup interval employed in this study was six months, which maximized the effects of treatment. However, it is probable that while improvement in the substance abuse, medical, and even psychological problem areas is possible within that time period, improvement in the employment, family, and legal problem areas may have a longer latency. In addition, improvement in these areas may depend upon continued control of the substance abuse problem. While this suggests the possibility that greater relationships would be seen between the substance abuse measures and the other problem areas at a longer followup period, the data also argue that the reduced substance abuse may be necessary but not sufficient for improvement in these other areas. In fact, two-year followup data on alcoholics by Finney et al. (1980) support this conclusion, and point out the importance of posttreatment family and social variables in maintaining posttreatment gains.

Implications

The present data indicate that although it is tempting to ask whether patients are generally improved following treatment, it seems more reasonable to consider the specific treatment problems presented at admission, and the particular areas that have (and have not) shown improvement. In this regard, it seems clear that followup evaluations which report only the proportion of patients who have remained abstinent do not offer adequate information regarding the total effects of rehabilitation treatment.

With regard to the clinical implications of these data, it seems clear that the results support a move away from addiction-centered

therapy toward the development of more comprehensive programs offering counseling, therapy, and referral in a variety of potential problem areas. It may be that the general improvements reported by many evaluation studies are due in part to the specific effects of the associated services (e.g., job referral, family counseling) provided by most treatment centers, on the particular problems of their clients.

Importance of Psychological Dysfunction

Perhaps the most intriguing finding within the present results was the moderate general relationship shown, in both improvement scores and in outcome status measures, between the psychological area and the other problem areas. This finding is important for two reasons. First, the relationship between improvement in psychological adjustment and improvement in drug and alcohol abuse, may have implications for the etiologies of addiction. It has long been speculated that underlying psychological problems are the basis for many forms of addiction, and that chemicals of abuse may serve as medications for these underlying problems. Secondly, the general associations shown between psychological improvement and improvement in the other areas suggests that psychological interventions may be particularly important to the total rehabilitation effort within drug and alcohol programs. It may be that improvement in the psychological problems of addicted individuals has more pervasive and powerful effects on overall outcome than improvement in their substance abuse problems alone.

ACKNOWLEDGMENT

This work was supported by HSR&D Projects #284 and #525 from the Veterans Administration,

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A Preliminary Evaluation of Parenting, Depression, and Violence Profiles in Methadone-Maintained Women

S. M. Oehlberg, D. O'M. Regan, M. E. Rudrauff, and L. P. Finnegan

INTRODUCTION

Family Center is an outpatient day program for pregnant drug dependent women in the greater metropolitan area of Philadelphia. It is involved in both research and treatment. The program provides comprehensive services including obstetrical, medical, psychosocial, addictive, outreach, and aftercare.

The patients may be either self-referred or referred from other local drug programs when it has been ascertained that the client is pregnant. Clients maybe admitted to the program at any point in their pregnancy. Once admitted, the client is scheduled to be seen in the high-risk obstetrical clinic regularly until delivery. Following delivery, the patient remains in the program from three months to a year, depending on individual circumstances. Women may be maintained on methadone, if opiate dependent, or simply followed with respect to obtaining the best possible mental and physical health of mother and infant.

The potential for improved treatment of both mother and infant, especially prediction of problems, is extremely important. A pilot study was devised to explore three factors which were felt to be relevant to this: 1) degree of depression or abnormality of mood; 2) exposure to physical and/or sexual abuse; and 3) potential for child abuse or neglect.

Depression has been found to be a strong factor in the treatment of drug abusers (Beck et al. 1974; Beck et al. 1961; DeLeon et al. 1973; Weimann et al. 1978), and although a profile of personality characteristics with which to predict drug abuse has not been found, anxiety and depression were frequently present in addicts (Craig 1979a; Craig 1979b). Many possible variables indicated by previous studies and government publication of relevant demographics (Schneider et al. 1972; Smith et al. 1974; Spinetta and Regler 1972) were incorporated in tests to determine parenting ability and risk of child abuse.

An effort has been made to identify specific variables which would indicate, separately or in combination, those women who are likely to abuse or neglect their infants. The presence of severe depression, or abnormal mood states in the mother, and history of subjection to physical violence were selected as sources of possible predictors. The interrelationship between these factors, drug abuse, and parenting has also been considered.

METHOD

Subjects

Participants in the study were drawn from a population of clients at the Family Center Program and included drug dependent women who were abusing or had abused illicit drugs through the prenatal, intrapartal, and postpartal periods.

For the purpose of this pilot study, a sample of 21 pregnant women was drawn by consecutive presentation as new patients at the Center. Prerequisite for inclusion was methadone maintenance.

The resulting group consisted of 7 white and 14 black women, mean age 28.4 with a range of 20 to 39, mean age at first pregnancy 20.1 years. The mean number of living children was 3.0, with a range of 1 to 7. Eight subjects had completed high school; two had some college. Three subjects were currently employed part-time. Seven lived with their families of origin, ten with partners/husbands, two with both families of origin and partners/husbands, and two lived alone.

Materials

1) Profile of Mood States (POMS) measures mood within the time-frame of one week. There are six identifiable mood or affective states: Tension-Anxiety: Depression-Dejection: Anger-Hostility; Vigor-Activity: Fatigue-Inertia: and Confusion-Bewilderment. A Total Mood Disturbance score (TMD) is obtained by summing the six factor scores, weighting Vigor negatively (McNair et al. 1971).

2) Beck Depression Inventory consists of 13 items, rated on a four-point scale, zero to three, indicating depression levels of none to severe (Deck et al. 1974; Deck et al. 1961).

3) Violence Questionnaire quantifies violent events in the subject's past (e.g. beatings, rape). There are 23 items, yielding a possible score from 0 to 35, with a high score indicating a greater number of and/or more severe violent episodes. This questionnaire was developed by the Family Center staff.

4) Profile of Abuse/Neglect Risk Factors (PAF) evaluates potential for child abuse/neglect. It contains 90 questions, divided into psychosocial, pregnancy data, and parenting sections. This test was developed by the pediatric nurse practitioner with the help of the Family Center staff.

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Procedure

The POMS, Deck, and Violence Questionnaire were completed by the patient. The PAF was filled out by the primary social worker with the patient in attendance. Tests were administered at the initial interview or as soon thereafter as possible.

Weekly urine toxicologies were collected from all patients on a once-a-week, random day schedule. Urines were screened for methadone, morphine, quinine, stimulants, depressants, diazepam, and other contaminants.

RESULTS

In order to facilitate preliminary analysis of the data, certain items were selected from the PAP and the violence Questionnaire and used. to create a Life Event Scale (LES), Parenting Scale (PS), and High Risk of Abuse Scale (PAS). The individual items in these scales, total scores for the Violence Questionnaire, Peck, POMS, POMS subscores, urine toxicology results, and demographic data were compared by correlation [Table I].

Strong correlations were found to exist between the Deck and all of the POMS scores except Anger and Tension. Total POMS scores also correlated with the LES and presence of amphetamines in the urine, while POMS Confusion and Fatigue scores correlated highly with presence of depressants in the urine. POMS Tension scores also correlated with the LES [Table I].

The prenatal clinic attendance was correlated at a significant level with depression, parenting, total urine toxicologies, and depressants in the urine, parity, and age. RAS scores correlated only with presence of amphetamines in the urine. LES scores correlated with PS scores, which were also related to employment and education, age, parity, and depressants in the urine [Table I].

An incidence of reported rape of 52 percent was noted, with 3 of 11 raped or molested by a relative. It is interesting to note that these three subjects scored particularly high on the Total POMS and the Beck [Table I].

Urine toxicologies throughout the pregnancy and postpartally revealed that 50 percent of all the urines collected from these-contained significant amounts of drugs other than methadone. Depressants (morphine, diazepam) accounted for 44 percent, and amphetamines for 8 percent of the total number of urinary contaminants [Table I].

DISCUSSION

Review of the findings reveals many ares which merit further study and analysis. A larger sample would yield greater reliability; while more informtion about the general character of drug abusers, rather than only methadone maintained subjects, would be worthwhile.

TABLE I

SIGNIFICANT CORRELATIONS

Parenting	:	Age	-.53**
	:	Parity	-.71***
	:	Employment/Education	.57**
	:	Depressants	-.61**
	:	Life Events	-.60**
	:	Prenatal Clinic Attendant	.68***
Life Events	:	Urine Toxicology	.50**
		POMS Total	.43*
		POMS Tension	.46*
High Risk of Abuse	:	Amphetamines	.51*
Beck Depression	:	Prenatal Clinic Attendance	-.57**
	:	POMS Total	.61**
	:	Depression	.62**
	:	Vigor	-.57**
	:	Fatigue	.58**
	:	Confusion	.60
POMS Confusion	:	Depressants	.47*
POMS Fatigue	:	Depressants	.57**
Urine Toxicology	:	Prenatal Clinic Attendance	-.48*
	:	Employment/Education	-.61**
Prenatal Clinic Attendance	:	Depressants	-.57**
	:	Parity	-.55**
Employment	:	Age	-.49*

* $p < .05$
** $p < .01$
*** $p < .001$

Correlational comparisons are valuable in looking for relationships, but multiple regression, principal component, and discriminantanalyses are needed in order to determine whether the reare indeed predictive qualities present.

Depression and Mood

In the total Family Center population, we have observed that high depression scores on admission predispose a client to drop out, continued drug use, and indications of poor attachment to the infant. Depression scores correlated negatively with attendance at prenatal clinic. This may be explained by its tendency to immobilize and limit ability to follow through on activities.

The effects of chemical depressants or stimulants may well be confusing the results with regard to depression and mood states. The presence of depressants in the urine also correlated with the total POMS scores.

Positive correlations between the Tension and Total POMS scores and the LES scores are easily accepted as all the selected life events are traumatic and would naturally produce tension and contribute to raised levels in other POMS scales.

Exposure to Physical or Sexual Abuse

There seems to be an unusually high incidence of physical or sexual abuse, especially rape, present in the lives of these subjects; however, a comparable control group is needed.

Potential for Child Abuse or Neglect

The only correlation with the RAS scores was with presence of amphetamines in the urine. These subjects, however, were not known to abuse their other children.

Parenting

While parenting scores did not relate to child abuse, they did correlate with some demographics: maternal age, number of children, education, and employment. Higher age and number of children may be confounding variables as well as independently limiting ability to parent (in drug abusers). Both education and employment open avenues for personal growth; spending time away from children; and obtaining information pertaining to child care, development, discipline, and other parenting behaviors.

The percentage of depressants in the urine correlated negatively with total parenting scores. The effects of depressants would logically interfere with most behaviors relating to parenting.

The negative relation of LES saxes and parenting scores suggests that exposure to traumatic events makes it difficult, if not at times impossible, to carry out the pervasive responsibility of

parenting successfully.

Attendance at prenatal clinic correlated positively with total parenting scores. This suggests that evidence of positive maternal behaviors prenatally is indicative of strong potential for attachment and good parenting behaviors following delivery.

CONTINUED INVESTIGATION

We are continuing to collect data as described in order to achieve greater reliability. We need more methadone-maintained subjects, as well as new groups of non-methadone-maintained drug abusers, and non-drug abusers for comparison.

Addition of the Hamilton Rating System for Depression and The Tennessee Self-Concept Scale will broaden the range of investigation into personality factors. Moreover, serial measurements would assist us in picking up variations in individuals.

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Granting Dose Increases to Methadone Maintenance Patients: Effects on Symptomatology and Drug Use

M. Stitzer, G. E. Bigelow, and I. Liebson

The goal of methadone maintenance treatment is to stabilize patients on a daily dose of methadone which allows them to feel comfortable and function adequately, while the cross tolerance conferred by methadone reduces opiate-seeking behavior. Low maintenance doses are generally considered desirable since these provide fewer discriminable drug effects and may make it easier for patients to ultimately detoxify and become drug free.

In practice, havever, there are few rational guidelines for selection of a methadone stabilization dose for a given patient. Treatment clinics generally select individual doses from a range which is currently considered optimal (30-80 mg), but doses may frequently be adjusted in response to patient complaints, and negotiation for dosage adjustments can take up considerable time and attention of treatment staff. A previous report (Stitzer and Bigelow 1976), describing dosage alterations among methadone maintenance patients enrolled in treatment for a full year, found that only 12.1 percent of patients were maintained at a single dose for the entire time, while the majority (63.6 percent) had dose alterations (up and down) which cumulated to 30 mg or less of dose change per patient per year. Dose increases of 5-10 mg were common, and several of these might be granted to an individual patient during a year of treatment.

The utility of small dose alterations in patients maintained on and tolerant to methadone is questionable. Previous studies (Berry 1972; Garbutt and Goldstein 1972; Goldstein and Judson 1973) concluded that clinical outcomes were essentially indistinguishable for patients maintained at widely disparate stabilization doses between 30 and 160 mg. Assessment of the effects of chronic dose alterations, however, is relevant to the clinical problem of dosage selection for individual patients. In particular, it would be useful to determine whether dose increases can effectively enhance patient comfort. The present study examined the effects of blind 20 mg dose increases which were granted to patients with persistent complaints about their methadone dose. The purpose of this study was to determine whether a dose increase of this magnitude would

have any detectable effect on symptomatic complaints or supplemental drug use.

METHODS

Clinic procedures. Maintenance patients report to the clinic daily and ingest their daily dose of methadone at the clinic dispensary under nursing supervision. Doses are dispensed as Methadose in a cherry syrup drink made up to a volume of 60 cc. Informed consent had been obtained from all patients for blind dose adjustment procedures. Patients could formally request a dose increase at any time by meeting with a staff member and stating the specific physical symptoms or complaints which led to the request for increase. Patients were told that any dose increases granted would be blind, and they were encouraged to continue requesting increases if symptoms did not abate. Blind dose increases which occurred during this study were made abruptly in a single day with the volume of cherry syrup drink raining constant.

Subject selection. A total of 99 increase requests were made by 50 patients enrolled in this treatment clinic during the first 15 months the procedure was in effect. Twenty-two patients (44 percent) filled out at least one dose increase request: however 66.7 percent of all requests were made by only six patients, each of whon trade six or more requests. These six patients were selected for participation in the present study, as were two additional patients (DJ, DZ) who were maintained at a relatively low methadone dose (30 mg) and had a relatively high level of symptom complaints, but who did not specifically request dose increases.

Subject characteristics. Participants in the present study, all males, had an average age of 27.3 years (range 22-31 years) and reported an average of 8.8 years of prior narcotic addiction. All were Caucasian but one (DZ), who was black, and all but DZ were recent program admissions, having been enrolled in treatment an average of 5.9 weeks (range 1-17 weeks) prior to the start of data collection for this study. Average methadone dose for study participants was 46.3 mg (range 30-60 mg).

Measures. Symptom complaints were assessed using a 59-item symptom checklist from which 56 items were scored. The checklist contained symptoms specifically related to methadone withdrawal and methadone side effects as well as items designating general psychological and miscellaneous physical complaints. For each item, subjects checked one of four possible answers according to the level at which they experienced the symptan during the previous 24 hours: 0 = not at all; 1 = slight; 2 = moderate; 3 = severe. The total score reported represents the sum of scores on each item. Patients completed symptom reports twice weekly on Monday and Friday or daily if they wished following a dose increase request until they felt their dose was adequate.

Supplemental drug use was assessed from TLC analysis of urine samples collected twice weekly on Monday and Friday. All samples

were routinely analyzed for methadone, opiates (heroin, morphine, codeine, meperidine, hydranorphone), barbiturates (phenobarbital, unspecified barbiturates), nonbarbiturate sedatives (meprobamate, methaqualone, glutethimide, ethchlorvynol), stimulants (cocaine, amphetamine, methamphetamine, phenmetrazine) and phenothiazines, phenytoin and propoxyphene.

RESULTS

Symptom complaints. As shown in Fig. 1, total symptom complaint scores were suppressed following the dose increase in 6 of 8 subjects (DZ, DJ, BB, HD, DH, BH), while two others (KM, VC) did not show any clear alterations in symptom complaints. A matched pairs *t*-test was used to compare average symptomatology scores obtained for each study participant during three weeks before and three weeks following the dose increase. The test revealed a significant reduction in symptomatology scores for the group as a whole ($p<0.01$).

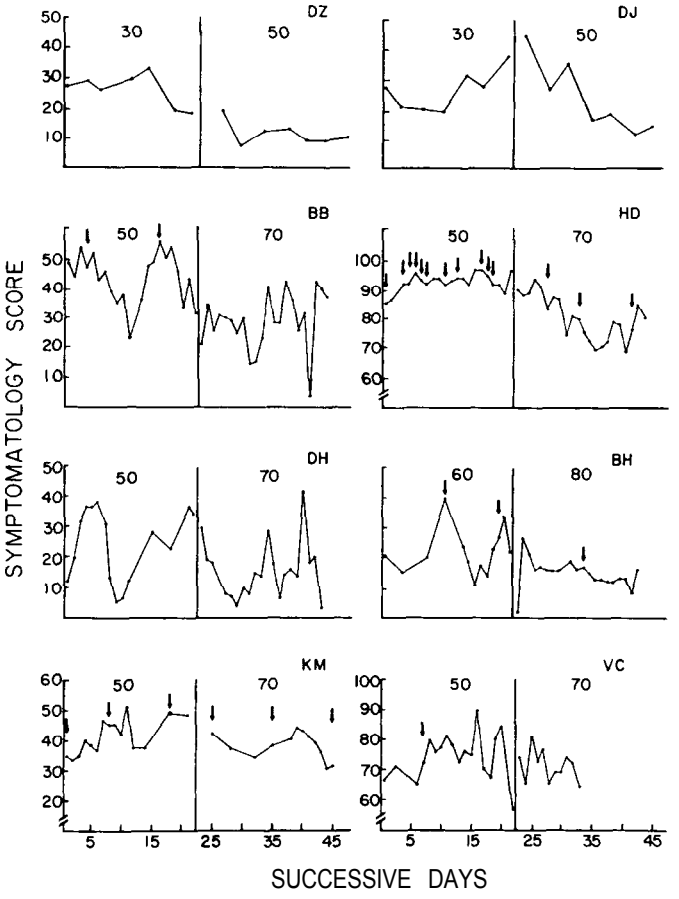
Although reductions in symptcmatology were noted within one week following a dose increase, these effects did not always persist. For some patients (e.g., subjects DH, BB in Fig. 1), complaints tended to return to previous levels within three weeks following the dose increase. The tendency for recurrence of high levels of symptom complaints can be seen more dramatically in Fig. 2, which shows symptomatology data for subjects BB and HD over several months time. Symptomatology scores repeatedly returned to high levels following dose increases, and these patients continued to make occasional dose increase requests. Reduced symptomatology scores did persist, on the other hand, for subjects DZ and DJ, whose doses were increased from 30 to 50 mg.

Urinalysis reports. Urinalysis results shown in Table 1 reveal that all subjects except DZ habitually used a variety of supplemental drugs in addition to their methadone. Table 1 also shows that there were no systematic changes in urinalysis results for the barbiturate, benzodiazepine or other drug categories during the three weeks after the dose change compared to the three weeks prior. Of the three patients who had been abusing supplemental opiates, however, two (HD, DZ) had substantial reductions in opiate positive tests after the dose increase.

DISCUSSION

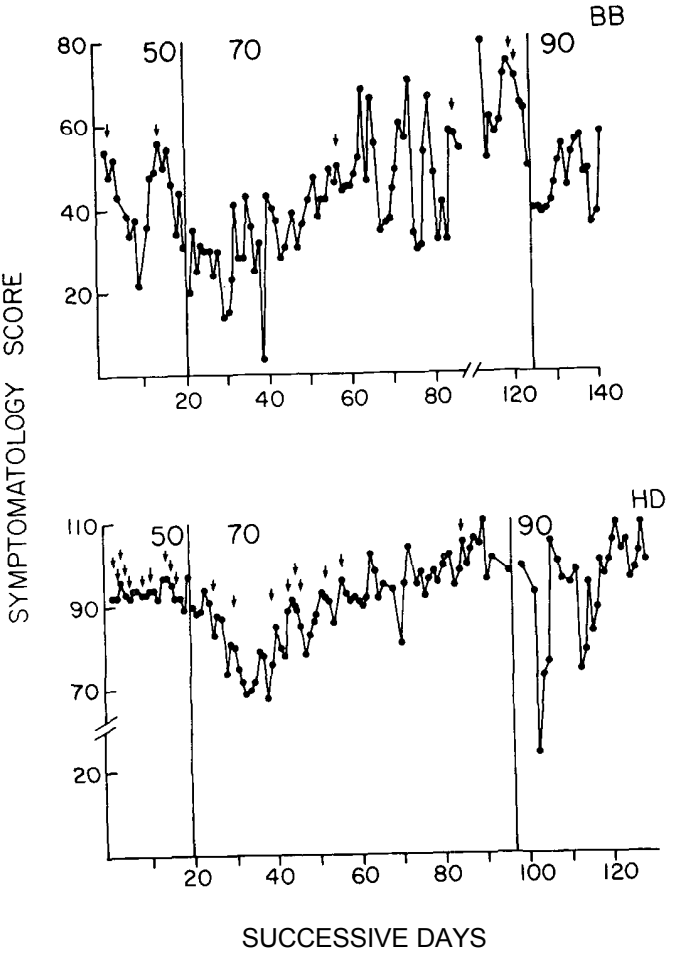
Results of the present study suggest that dose increases may have at least short-term beneficial effects on symptomatology (Fig. 1) and opiate drug use (Table 1) in methadone maintenance patients who complain about their dose. On the other hand, the long-term benefit of dose increases is questionable since the effects on symptomatology tended to be transitory in many subjects, with high levels of complaints recurring over time even after repeated dose increases (Fig. 2). Furthermore, use of supplemental sedatives and tranquilizers was unaffected by the dose increase procedure. The results of this experiment confirm and extend to a within-

FIGURE 1



Symptomatology scores in eight individual methadone maintenance patients are shown before (left-hand panel) and after (right-hand panel) an abrupt 20 mg dose increase. Methadone dose (mg) is indicated within each panel. Vertical arrows indicate days on which the patients requested a dose increase. Derivation of total symptomatology scores is described under Methods.

FIGURE 2



Symptomatology scores are shown for two individual patients maintained at three successively higher methadone doses. Methadone dose (mg) is indicated within each panel of the figure. Vertical arrows indicate days on which the patient requested a dose increase.

TABLE 1

Percent Positive Urines

Subject	Before Dose Increase				After Dose Increase			
	Op[1]	Barb[2]	Other[3]	Benzo[4]	Op	Barb	Other	Denzo
DZ	50.0	0	0	0	0	0	0	0
DJ	83.3	0	0	66.7	66.7	0	0	100.0
BB	0	0	100.1*	100.0	33.3	0	83.3*	100.0
HD	66.7	33.3	66.7	100.0	0	0	83.3	100.0
DH	0	0	33.3	100.0	0	50.0	33.3	100.0
BH	0	16.7	33.3	100.0	0	50.0	66.7	100.0
KM	0	0	0	100.0	0	0	16.7	66.7
VC	16.7	33.3	16.7	100.0	0	0	33.3	100.0

[1] *Opiates include morphine and demerol.*

[2] *Barbiturates (unspecified)*

[3] *Except as noted, other drugs include methaqualone, ethchlorvynol and phenothiazines.*

[4] *Benzodiazepine tranquilizers*

[*] *Propoxyphene*

subject analysis reports (Berry 1972; Berry and Kuhn 1973; Garbutt and Goldstein 1972; Goldstein and Judson 1973) of no differences in clinical outcomes for methadone patients maintained on widely different methadone doses, except for reduced opiate use at higher doses.

It could be argued that continued use of supplemental drugs, including sedatives and minor tranquilizers, would make these particular methadone patients relatively insensitive to alterations in their methadone dose. This argument may have merit. Nevertheless, these particular patients were considered appropriate for evaluation of the dose increase procedure because of their persistent requests for dose increases. The association of supplemental drug use and requests for dose increases in these patients suggests that the latter may be part of a generally high level of drug seeking behavior in these particular patients.

Findings from the present study are relevant to current clinical practice regarding dosage selection and adjustment. They suggest that raising doses which are already above 30 mg may have at best a temporary effect on complaints and may have no effect on supplemental polydrug use. If dose increases of 20 mg have little effect, the common practice of granting smaller dose increases on the order of 5-10 mg may have even more questionable utility. Furthermore, to the extent that dose increases are detectable, they may serve to reinforce persistent complaints and continued requests for dosage adjustments, thus exacerbating the problem they are meant to correct.

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ACKNOWLEDGMENT

This research was supported by National Institute on Drug Abuse grants 5 R01 DA-01472 and 5 KO2 DA-00050.

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The Effect of Heroin and Naloxone on the Growth of Neuroblastoma Tumors in Mice

I. S. Zagon

INTRODUCTION

Although narcotic drugs are best-known for their analgesic and behavioral effects, these agents have also been reported to be cytotoxic (Roizin and Liu, 1977), antimitotic (Andersen, 1966), and to retard growth and development in many diverse organisms and cell types (Willson et al., 1976; Zagon and McLaughlin, 1977a, b, 1978).

In view of the growth-impeding properties of opiates in normal tissues undergoing proliferation and development, we were prompted to examine whether these compounds are also effective in inhibiting the growth of tumors. In the present study we have determined the effects of heroin on C1300 murine neuroblastoma, a well-characterized tumor system that resembles human neuroblastoma in many respects (Finkelstein et al., 1973). Drug injections were initiated prior to tumor cell inoculation in order to assess whether animals exposed to heroin before tumor induction exhibit alterations in their capacity to develop tumors, as well as in tumor growth and survival time.

METHOD

Animals. Male syngeneic A/Jax mice (6-8 weeks of age)were obtained from The Jackson Laboratories, Bar Harbour, ME. Groups of 5 male mice were housed in stainless-steel cages and given water and Purina laboratory chow ad libitum.

Tumors. The murine tumor cells, S20Y neuroblastorna, cloned from the A/Jax mouse C1300 neuroblastoma, were obtained from Dr. M. Nirenberg, (NIH, Bethesda, MD). Cells were grown in Dulbecco's medium containing 10% fetal calf serum and 0.225% sodium bicarbonate in an atmosphere of 5% CO_2/95% air at 37°C. Cell viability was determined by the trypan blue exclusion test.

To induce tumor formation, 10^6 cells in 0.05 ml growth medium were injected s.c. just posterior to the dorsal surface of the right

foreleg; this area had been shaved previously with electric clippers. The day of tumor cell inoculation was considered Day 0.

Body weights of mice were recorded on a weekly basis. Tumor size was measured in 2 dimension with vernier calipers (accuracy, 0.05 mm) on a biweekly basis (every 3rd and 7th days). Since tumors grew in somewhat irregular shapes, the largest dimensions perpendicular to one another were always chosen; an approximtion of tumor diameter was obtained by averaging the two measurements for each animals. The time of "initial appearance" of a tumor was considered the day at which tumor diameter was 5 mm or larger. At death, a random sampling of mice from each treatment schedule was autopsied for metastases.

Drug Treament. Forty mice were divided into 4 groups of 10 animals each. Some mice received daily s.c. injections of either 6 mg/kg heroin (diacetylmorphine; National Institute on Drug Abuse, Bethesda, MD) or 0.1 ml sterile saline (= heroin-tumor and saline-tumor groups, respectively). In addition, another group of mice received daily s.c. injections of naloxone (10 mg/kg; Endo Laboratories, Garden City, NY) simultaneous with the heroin injections (= heroin-naloxme-tumor group). Two weeks after the initiation of drug injections, these groups of mice received tumor cell inoculations. Inorderto control for the effect of heroin on bodyweight and mortality, another group of mice that had receiving heroin was injected with only growth medium (= heroin only group). Drug or saline injections were continued until the death of all tumor-bearing animals.

Statistics. Tumor size was analyzed at 3- or 4-day intervals an post-inoculation days 10-31 using an analysis of variance with the 7 measurement points analyzed as a repeated measure. This time period corresponded to one in which 50% of all mice were alive. Tumor size on the day of death, as well as survival times of tumor-bearing mice, were also analyzed using an analysis of variance; subsequent analyses to determine differences between Treatment schedules were performed with the Newman-Keuls test. P values less than 0.05 were considered significant.

Body weights of mice were compared a two-factor analysis of variance. Treatment Schedule was considered to be a between-group variable and Days (10-31) was a within-group variable.

RESULTS

General Observations. Within three weeks after the injection of neuroblastma cells, all mice in the saline-tumor and heroine-naloxone-tumor group had developed measurable tumors. In contrast to these results, 2 of the 10 mice in the heroine-tumor group did not develop tumors within the 62 days after cell inoculation. Metastases were not observed in drug- or saline-treated mice inoculated with neuroblastma. Body weights did not differ between any group of mice.

Survival Time. Mean survival time of mice in the heroin-tumor group was extended 35% in comparison to controls, and mediam survival time for tumor-bearing mice receiving heroin was extended 18%. Although mice in the saline-tumor group began to die in the 4th post-inoculation week and 100% of these mice had died by the 6th week, the first death in turmor-bearing mice treated with heroin occurred on day 34 and some of these mice lived more than 3 weeks beyond any of the mice in the saline-tumor group. Animals receiving simultaneous injections of heroin and naloxone did not differ significantly from saline-tumor mice in mean survival time, nor were major differences noted in either the median or range of survival time.

Tumor Growth. In contrast to saline-tumor mice,the mean time for the initial appearance of measurable tumor was delayed by 45% in mice of the heroin-tumor group. The median time of tumor appearance was comparable for heroin-tumor and saline-tumor groups. Whereas 100% of saline-tumor animals had measurable tumors by day 10, tumors in all of the heroin-tumor mice were not observed until day 24. Tumor growth between days 10 and 31 was significantly retarded in mice of the heroin-tumor group, with marked reductions found on days 17, 21, 24, 28, and 31. At the time of death, animals in the heroine-tumor group also had smaller tumors than mice in the saline-tumor group, with a mean reduction of 21% being recorded for tumor-bearing animals receiving heroin.

A 23% delay in the mean time for the initial appearance of tumors was observed for mice in the heroin-naloxone-tumor group, but the median day for initial tumor appearanace, tumor growth between days 10 and 31, and tumor size at death were comparable to controls.

DISCUSSION

The results of this investigation show that administration of heroin, beginning 2 weeks prior to tumor cell inoculation, delays the initial appearance of measurable tumors, retards tumor growth and prolongs survival time in mice with transplanted neuroblastoma tumors. Moreover, despite inoculation with 10^6 cells, which was found in this study and others (Shuffler, Repman, and Schengrund, 1979) to induce neuroblastoma in 100% of the controls, sane heroin-injected animals never developed tumors within the 62-day post-inoculation period; this would suggest that heroin may also suppress the formation of tumors.

The dosage of heroin utilized in this study was not exceedingly high, being above the analgesic dose of 1 mg/kg, but well below the LD_{50} level of 190 mg/kg (Brands, Hirst, and Gowdey, 1975) in mice. Tumor-bearing animals receiving heroin also did not lose bodyweight, incontrast to the cachexia observed with many of the antitumor agents, again reflecting the low general toxicity of the dosages employed.

The mechanisms underlying heroin's ability to retard tumor growth and prolong survival are presently unclear. Heroin's action does appear to be related to certain physiological properties of opiates

since administration of naloxone, a well-known opiate antagonist, blocked heroin's antitumor activity. Opiates have been reported to suppress cell division, alter polyamine, nucleic acid and protein biosnythetic systems, and retard growth (Andersen, 1966; Roizin and Liu, 1977; Slotkin, Seidler, and Whitmore, 1980; Willson et al., 1976; Zagon and Mclaughlin, 1977a, b, 1978). One or me of these actions may be responsible for heroin's effects on neoplasia.

Narcotic analgesics such as heroin are commonly used in the control of pain in patients with advanced stages of malignancy (Ettinger, Vitale, and Trump, 1979; Twycross, 1974). In view of the present data, it appears that some opiates, in addition to their analgesic and behavioral properties my also alter cell function and response associated with oncogenesis.

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ACKNOWLEDGMENTS

Supported by NIDA grant DA-01618.
The technical assistance of Patricia J. McLaughlin is gratefully acknowledged.

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Quantum Chemical Studies of the Origin of Agonist and Antagonist Activity in 3- and 4-ΦPiperidines

G. H. Loew, S. K. Burt, and G. M. Hashimoto

A number of 3-arylpiperidine compounds are now known which possess potent opiate narcotic analgesic activity and which exhibit antagonistic activity (Kugita et al. 1965, Iorio and Casy 1978, Jacoby et al. 1974). All compounds with a 2-CH_3 substituent and ,a mOH group on the phenyl ring are potent, pure antagonists, regardless of their N-substituent. In contrast, the few compounds reported without a 2-CH_3 group are mixed agonist/antagonists. Thus this class of opiates exhibit structure-activity profiles markedly different from the rigid opiates.

TABLE I: CALCULATED LOW-ENERGY ISOMERS AND OBSERVED PHARMACOLOGICAL ACTIVITY FOR 3-OPIPERIDINES

3-R	2-R	Low-Energy Isomers	Activity (Agonist/Antagonist)		
			NO OH	mOH	pOH
CH_3	H	O_{EQ}, N-R_{EQ}; O_{AX}, N-R_{EQ}	ND	WK AG/ND	ND
	α-CH_3	O_{EQ}, N-R_{EQ}; O_{AX} N-R_{EQ}	ND	INACT/ANT	ND
	β-CH_3	O_{EQ}, N-R_{EQ}	ND	INACT/ANT	ND
COOEt	H	O_{EQ}, N-R_{EQ}	AG/INACT	AG/ANT	WK AG/INACT
	α-CH_3	O_{EQ}, N-R_{EQ}	------ ND ------		
	β-CH_3	O_{EQ}, N-R_{EQ}	------ ND ------		

Recently potent pure antagonists with a mOH-0 in the 1,3,4-trialkyl-4-phenylpiperidine series were prepared (Zimmerman et al. 1978a, Zimmerman et al. 1978b). In this series, antagonism was not found to be modulated by N-substituent variation. The structure-activity profile for a number of these analogs indicates that the 4-R group, the 3-CH_3 substituent, as well as the position and presence of a phenolic hydroxyl are all modulators

of agonist/antagonist potency. These compounds, then, also have a very different structure-activity profile from the rigid opiates. The study of molecular features of opiates that regulate the extent of agonism/antagonism in a given opiate are particularly suited to quantum mechanical calculations since the ratio of agonism to antagonism should be a receptor-related event and should be reflected in molecular indices obtained from conformational calculations and electronic properties.

TABLE II: CALCULATED LOW-ENERGY ISOMERS AND OBSERVED PHARMCOLOGICAL ACTIVITY FOR 4-0PIPERIDINES

4-R	3-R	LOW-ENERGY ISOMERS	ACTIVITY (AGONIST/ANTAGONIST) NO OH	mOH
CH_3	H	0_{EQ}, N-R_{EQ}; 0_{AX}, N-R_{AX}; 0_{EQ}, N-R_{AX}	WK AG/INACT	AG/INACT
	a-CH_3	0_{EQ}, N-R_{EQ} 0_{AX}, N-R_{EQ} ;0_{EQ}, N-R_{AX}	INACT/INACT	WK AG/WK ANT
	β -CH_3	0_{EQ}, N-R_{EQ}	INACT/WK ANT	INACT/ANT
n -C_3H_7	H	0_{AX}, N-R_{EQ}	AG/INACT	AG/INACT
	α-CH_3	0_{AX}, N-R_{EQ}	INACT/INACT	AG/INACT
	β -CH_3	0_{EQ}, N-R_{EQ}	AG/INACT	WK AG/$^{POT}_{ANT}$
$OCOC_2H_5$	H	0_{EQ}, N-R_{EQ}; 0_{EQ}, N-R_{AX}	AG/INACT	ND
	α-CH_3	0_{EQ}, N-R_{EQ}; 0_{EQ}, N-R_{AX}	AG/INACT	ND
	β -CH_3	0_{EQ}, N-R_{EQ}	AG/INACT	INACT/ANT

In order to understand their unusual structure-activity profile, determine their molecular requirements for agonism and antagonism, and to suggest new, potentially useful analogs for synthesis and testing, we have calculated the energy-conformation behavior of the series of 3- and 4-0piperidines given in Tables I and II, using the semiempirical quantum mechanical method called PCILO (Diner et al. 1969).

For each possible geometric isomer, nested rotations were performed around all torsional axes and local geometry optimizations made for minimum rotational conformers. The conformational results obtained should be essentially the same for m- and p-OH, but not necessarily o-OH, substituents on the phenyl ring.

The low-energy isomers obtained for all analogs studied are summarized in Tables I and II. While some isomers of the des-CH_3 compounds had conformational flexibility, all eight isomers of the 2-CH_3, 3-R, 3-hiperidines and 3-CH_3, 4-R, 4-0peridines had only one low-energy conformation. As shown in these tables, for both the 3- and 4-0piperidines, the same low-energy isomers were found for the des-CH_3 and a-CH_3 analogs; while the β-CH_3 compounds have different conformational behavior. Surprisingly, for the

des-3-CH_3, and α-3-CH_3, 4-n-propyl analogs, unlike any other known 4-0piperidines, an isomer with an axial phenyl ring is predicted to be the unique, low-energy form. An X-ray structure determination of these analogs should help verify these results.

The results of the energy-conformation studies, together with the known activity profile, allows the selection of 3-0 and 4-0 opiate pharmacophores--i.e., conformations and orientations at the receptor site--responsible for agonist and antagonist activity.

All of the 3-0piperidines studied have antagonist activity with a mOH group, and all have one and only one common low-energy isomer: 0_{EQ}, N-R_{EQ}. This isomer, in an orientation at the receptor site allowing interaction of the phenyl ring similar to rigid opiates, is thus proposed as the universal antagonist pharmacophore (Figure 1A, Pharmacophore I) for 3-0piperidines. The fact that a mOH creates the most potent antagonists reinforces this hypothesis.

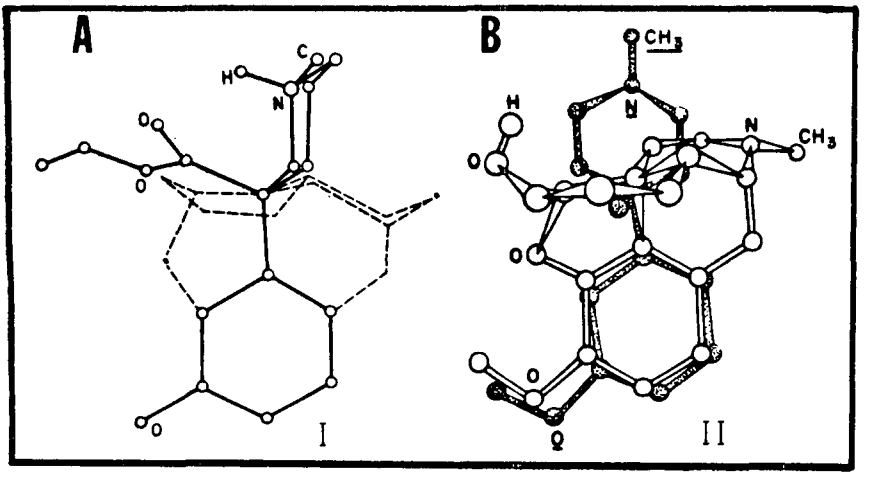

Figure 1: Proposed Antagonist Pharmacophores for A) 3-0piperidines and B) 4-0piperidines (shown against morphine for comparison)

The ß-isomers of all 4-0piperidine analogs studied also have only one low-energy isomer, 0_{EQ}, N-CH_{3EQ}. Moreover, for all of these compounds, a g-isomer is a pure antagonist when a mOH group is present. These combined results also clearly indicate a universal antagonist pharmacophore for 4-0piperidines: a 0_{EQ}, N-CH_{3EQ} isomer interacting at the receptor with a mOH-0 overlap similar to the rigid opiates (Pharmacophore II, Figure 1B). In these similar pharmacophores, the postulated role of the mOH group is to anchor a low-energy 0_{EQ}, N-R_{EQ} isomer in a phenyl overlap (antagonist) orientation at the receptor site.

Our results have thus allowed the selection of a universal antagonist pharmacophore for the 3-0piperidines and for the 4-0piperidines. The β-3-CH_3 isomers of both 3- and 4-0piperidines

with a mOH would all be pure antagonists, and the behavior of des-CH_3 and α-CH_3 isomers in general should be different from the B-isomers and similar to each other. These results are consistent with the observation of agonism in the des-CH_3 and α-CH_3 analogs but not in the β-CH_3 compounds.

Two remaining questions are: What is the origin of agonist activity in *3*- and 4-0piperidines with a mOH? What is the role of the mOH in modulating agonism and antagonism? Unlike the single an tagonist mode postulated for the 3- and 4-0piperidines (Figure 1A, B), there are a number of possible pharmacophores for each of these classes of opiates which could account for their agonist activity.

From our results for the 3-0piperidines, two different agonist modes seem possible (Figure 2A,B), one common to all 3-0piperidines (Pharmacophore III, Figure 2A) and one involving a boat conformer (Figure 2B) which our calculations indicate is possible only for des-2-CH_3 and a-2-CH_3, 3-CH_3, 3-0piperidines and not for any 3-$COOC_2H_5$, 3-0piperidines. Each proposed pharmacophore has an amine group interaction at the receptor site similar to fused ring opiates--a postulated key requirement for agonism.

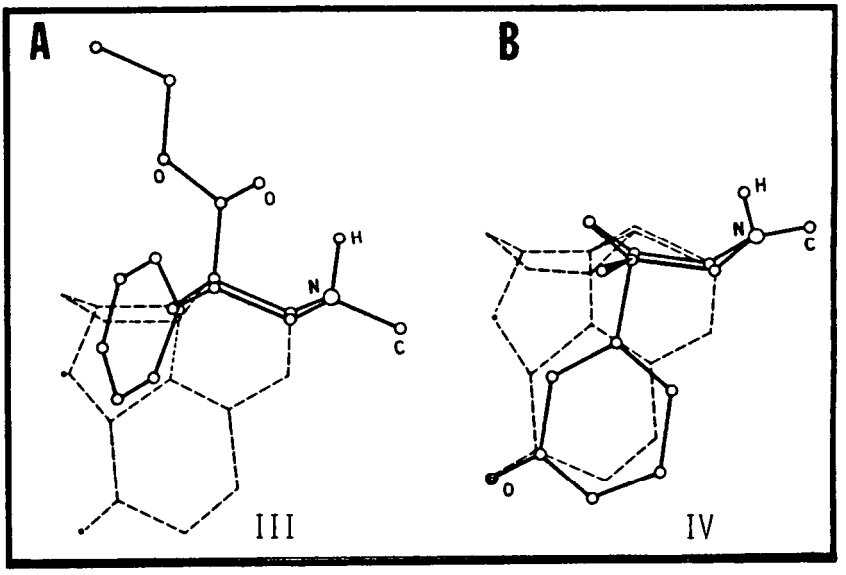

Figure 2: Proposed Agonist Phamacophores for 3-0piperidines

The agonist Pharmacophore III (Figure 2A) is proposed in addition to the antagonist mode as an alternative mode of interaction of the single low-energy conformer of the des-2-CH_3 betameperidines with the receptor site as a plausible explanation of its mixed agonist/ antagonist behavior.

This same pharmacophore could also be responsible for the agonist activity observed in 2-des-methyl, 1,3-diCH_3, 3-0piperidines, since the axial phenyl group of the low-energy 0AX, N-CH_{3EQ} isomer of this analog would occupy a similar position to the axial ester chain in Figure 2A. In this pharmacophore, the ester chain, or 0 group, is in the position of the C_{14}-OH group in oxymorphones or the C_9 extended group of the recently synthesized benzomorphans, substituents which appear to be interacting at a newly-delineated subsite of the opiate receptor which also modulates their relative agonist/antagonist activity.

If Pharmacophore III (Figure 2A) is responsible for agonism in the des-2-CH_3 analogs, the effect of adding a 2-CH_3 group on agonism can be predicted. The **β**-2-CH_3 isomer of betameperidine (2R, 3R) should retain agonism since the axial 2-CH_3 group in this position should not interfere with agonist-type binding if there is a receptor pocket available to them. The B- (2S, 3S) and **α**-isomers, which have an equatorial 2-CH_3 group in the position of a C_9 or C_{16} substituent in morphine, should not bind in the agonist mode (Pharmacophore III) and would be pure antagonist (Pharmacophore I). Synthesis and testing of 2-CH_3 analogs of betameperidines would verify this prediction.

For the des-2-CH_3, 3-CH_3, 3-0piperidines, both the chair and boat forms (Figures 2A,B) are possible conformers. Each predicts a different effect of addition of a 2-CH_3 group. If the chair form is a relevant one, the **α**-2-CH_3 isomers could retain agonism, since axial 2-CH_3 groups in these positions should not interfere with this agonist-type binding if there is a receptor pocket available for them; while B-isomers would not bind in this mode. If the boat form is the agonist, addition of a **β**-2-CH_3 group does not allow it and would result in a lack of agonist activity. For the a-isomer, while a boat form is possible, the 2-methyl group is in the position of the C_9 or C_{16} substituent as in morphine, blocking activity.

For the 3-CH_3-3-(mOH)-0 analogs, both **α**- and **β**-2-CH_3 compounds have been synthesized. No agonism has been reported for either isomer. A piperidine boat conformer is then more consistent with the known effect of a 2-CH_3 group than the piperidine chair conformer. In this pharmacophore there is simultaneous overlap with both the amine nitrogen and the mOH-0 group of rigid opiates, suggesting agonist/antagonist potency ratios should be modulated by N-substituents--a hypothesis that could be tested by the synthesis and testing of analogs with varying N-substituents.

From our results, agonist activity in the 4-0piperidines could be due to three types of pharmacophores, shown in Figure 3A,B,C. Figure 3A shows a 4-0piperidine in a low-energy @EQ, N-R_{EQ} conformer. This conformer with a mOH substituent is the postulated antagonist mode. However, without a mOH; it could orient at the receptor with piperidine ring overlap with rigid opiates leading to agonism provided the 4-R group can serve as an effective binding site. This condition seems to be fulfilled when 4-R is an ester chain (meperidine or prodine) or the **β**-3-CH_3 isomer of a long alkyl chain

(4-R = n-CH_3H_7), all of which are pure agonists without a mOH, but not when 4-R = CH_3. This latter analog can interact only in the antagonist mode (Figure 2B) with or without a mOH and does not require a mOH for antagonism, while all the prodines, meperidines, and the β-3-CH_3, 4-n-C_3H_7 analogs require a mOH group to change from an agonist (Figure 3A) to antagonist orientation (Figure 1B).

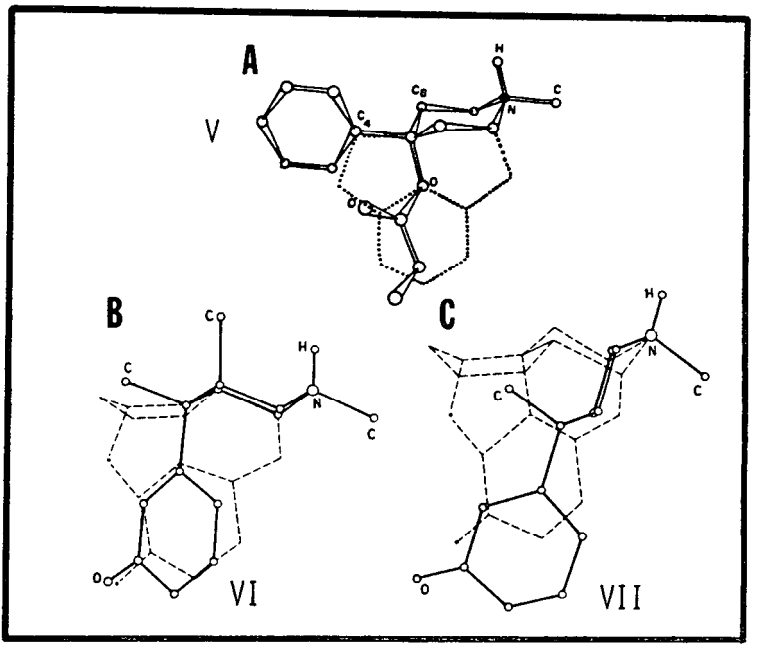

Figure 3: Proposed Agonist Pharmacophores for 4-0piperidines

Figure 3B shows a 4-0piperidine analog in a low-energy 0AX, N-R_{EQ} conformer. This conformer is the unique low-energy form for 4-R = n-C_3H_7 and probably for longer alkyl chain substituents with an α-3-CH_3 or no 3-CH_3 group. Thus this class of 4-0piperidines is predicted to have a similar structure-activity profile to rigid opiates; i.e., N-substituent variations should lead to potentially useful analogs with mixed agonist/antagonist behavior. This prediction is consistent with the observation that N-CH_3, α-3-CH_3, 4-n-C_3H_7, 4-0piperidine is a pure agonist, while the β-3-CH_3 analog (which can only be in Pharmacophore II conformation) is a pure antagonist.

The remaining des-3-CH_3 and α-3-CH_3, 4-R, 4-0piperidine analogs, in contrast to β-CH_3 compounds, are also predicted to have agonist as well as antagonist activity. However, the mixed agonist/antagonist activity when 4-R = ester chain is predicted to arise from interaction of another low-energy isomer, 0EQ, N-RAX, at the receptor site oriented as shown in Figure 3C (Pharmacophore VII). While these prodines have not been measured, the presence of two

low-energy isomers could explain the mixed agonist/antagonist behavior in the α- but not the β-isomers of 3-CH_3 ketobemidone. Since the pharmacophore shown in Figure 3C has some overlap with both the amine and phenyl group of rigid opiates, it is suggested that if agonism is observed in the des-CH_3 and α-CH_3 mOH prodines, it should be lessened by change of N-substituents from N-CH_3 to N-allyl of N-methylcyclopropyl.

For the 4-CH_3, 4-Opiperidines, the des-CH_3 and α-3-CH_3 isomers have three low energy conformers. One, in common with most 4-Opiperidines, could be responsible for antagonist activity (Pharmacophore II, Figure 1B), while either of the other two could lead to agonist activity. The O_{AX}, N-R_{EQ} conformer could bind in a Pharmacophore VI mode in common with the 4-n-propyl analogs (Figure 3B), while the O_{EQ}, N-R_{AX} isomer can bind in a Pharmacophore VII mode (Figure 3C), in common with one proposed for the prodines. In either of these pharmacophores there can be nearly simultaneous overlap with both the mOH-O and amine groups of rigid opiates. If the observed agonism of the α-analog of 1,2,3-trimethyl-3-(mOH)Opiperidine is due to binding in either mode, then variation in N-substituents should lead to mixed agonist/antagonist activity.

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ACKNOWLEDGMENT

Support for this work from NIDA Grant 2 RO1 DA 02622-02 and helpful discussions with and data from Drs. R. Willette and D. Zimmerman are gratefully acknowledged.

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DHHS Publication No. (ADM) 81-1058
Printed 1981