National Institute on Drug Abuse

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9

NARCOTIC ANTAGONISTS: NALTREXONE

PROGRESS REPORT

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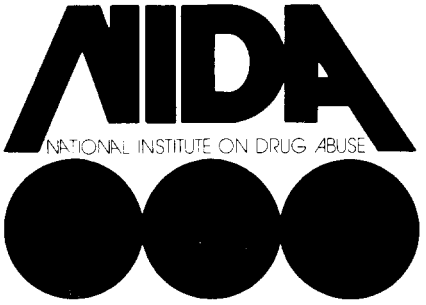
Division of Research
National Institute on Drug Abuse

September 1976

NIDA Research Monograph 9

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Alcohol, Drug Abuse and Mental Health Administration



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Rockwall Building 11400 Rockville Pike Rockville, Maryland, 20852

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NALTREXONE

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ACKNOWLEDGMENTS

The editors wish to thank the National Academy of Sciences' Committee on Problems of Drug Dependence for graciously encouraging the inclusion of a Satellite Conference on Naltrexone into its 38th Annual Scientific Meeting held in Richmond, Virginia on June 7th to 9th, 1976. They would like to thank Mr. Alex Bradford and his staff at Biometric Research Institute for masterfully organizing the successful naltrexone conference. It was from this conference, and the enthusiastic response and well conceived papers of the participants, that this research monograph was derived.

DHEW publication number (ADM) 76-387

Library of Congress catalog card number 76-40692

This document is for sale by National Technical Information Service
Springfield, Va. 22161
Order number: PB 255 833. Papercopy: $7.50; Microfiche: $2.25

FOREWORD

The Conference on naltrexone reported here represents another step in a carefully designed plan to develop better treatment methods for opioid dependence. The early theoretical foundations for the use of antagonists were laid down by Abraham Wikler in 1955, when he postulated that physical dependence on opioids provided a continually recurring "synthetic" need that was readily satisfied by the use of opioids, that withdrawal phenomena could be conditioned to environmental stimuli, and that such conditioning played an important role in relapse to drug use long after drug withdrawal was completed.

A decade elapsed before these views on the role ofopioids in the reinforcement of drug seeking behavior and of conditioning could be applied to treatment in a practical way. In a series of papers, beginning in 1965, William Martin and his co-workers at the Addiction Research Center at Lexington, Kentucky, presented the clinical pharmacology of cyclazocine, a long-acting, orally effective narcotic antagonist, and suggested the ways in which drugs like cyclazocine might be used in treatment. In essence, Martin and his colleagues pointed out that cyclazocine would block the effects of acutely administered opioids, that when cyclazocine was given daily even chronicopioiduse would not produce physical dependence, that tolerance did not develop to the antagonistic effects of cyclazocine, and that cyclazocine itself (while not as aversive as nalorphine), was not a drug likely to be abused. Thus, chronically administered cyclazocine had the potential of 1) blocking the positive reinforcement of drug seeking behavior permitting extinction to occur; 2) preventing the development of physical dependence, thereby eliminating relief of withdrawal as a source of reinforcement; and 3) preventing readdiction, permitting the phenomena associated with protracted withdrawal to undergo a gradual resolution. Lastly, the use of antagonists might prevent death from narcotic overdosage even if it did not eliminate drug seeking behavior.

The question of whether opioid addicts would voluntarily accept treatment with a drug like cyclazocine, which promised nothing other than to prevent them from feeling the effects ofopioiddrugs, was quickly answered. Jaffe and Brill in 1966 and Freedman et al. in 1967, reported their experiences with heroin addicts who volunteered to participate in treatment programs centered around the use of cyclazocine. It was apparent that there did exist a group ofopioid dependent individuals who, at some point, were motivated to become totally independent of the need for opioid drugs.

However, several problems became apparent in these early clinical studies-problems which are not yet entirely resolved, but which led directly to this conference and to our present state of knowledge. First, most of the subjects who volunteered for treatment with cyclazocine frequently neglected to take the drug on a regular basis; most dropped out of treatment within a few months, and by the time they were contacted many had relapsed to regular opioid use (usually heroin). Second, many addicts discontinued treatment complaining of the unpleasant side effects that cyclazocine produced. While such complaints often seemed to the investigators to be rationalizations, from a practical point of view it was difficult to persuade patients to continue with treatment. In order to test the conditioning theory and to determine if antagonists could play a useful role in treatment, better antagonists were needed, i.e., drugs that were freer of side effects and drugs that would have such a long duration of action that daily ingestion would be unnecessary. It was apparent that this was primarily a technological problem, and one that given time and money could be solved.

Thus, by 1967 the basic strategy that would be required to test the utility of narcotic antagonists in the treatment of opiate dependence was largely shaped. Although Freedman and Fink and their co-workers continued to explore the possibilities of using high doses of oral naloxone, a relatively pure antagonist, most investigators felt that its short duration of action and relative ineffectiveness by mouth limited its usefulness. In that same year, 1967, Blumberg and his colleagues reported on the effects in animals of a new oxymorphone-derived antagonist, EN-1639A, later to be called naltrexone. Naltrexone seemed to be the sought after antagonist--relatively free of agonistic activity, and with a longer duration of action than noloxone. Although the formal archival publications did not appear until 1973, at the 1971 meeting of the NAS/NRC Committee on Problems of Drug Dependence Martin, Jasinski and their co-workers reported that in post-addicts naltrexone was orally effective, long-acting and relatively free of side effects.

The effort to move naltrexone from these preliminary observations on a few patients at the Addiction Research Center at Lexington to the hands of clinical investigators where its efficacy might eventually be tested was given sudden acceleration when President Nixon created the Special Action Office for Drug Abuse Prevention (SAODAP) on June 17, 1971. Along with this office, established within the Executive Office of the President, came both the economic resources and the influence needed to speed up the development of narcotic antagonists. As the first director of SAODAP, I regarded the development of naltrexone as one of my high priorities. However, even if I had not felt that the development of naltrexone was worthwhile, I would have felt obliged nevertheless to bend every effort toward its clinical development. Influential members of Congress had become enthusiastic about the possibility of a non-dependence producing pharmacological alternative to the use of methadone. The Congress included in the legislation creating SAODAP a section on the development of antagonists along with appropriations to be used specifically for such development.

There have been numerous stumbling blocks along the way. Some of them related to supplies of thebaine, the precursor used in the manufacture of naltrexone, and the limited production of the drug. In addition, not wanting to place all bets on a single drug, SAODAP initiated research with other antagonists; and recognizing that eventually even the two to three day duration of action of naltrexone would prove to be too short, SAODAP also initiated the effort to develop long-acting depot preparations. Ultimately, money, people and experimental designs were combined in a manner required to produce the products and the data.

At various times over the past decade, as the effort to test the utility of antagonists progressed, I pointed out that despite their great theoretical promise, antagonists might prove to be of value for only a limited subgroup within the opioid using population. Yet, each of those times there seemed to be little alternative to getting on with the effort to subject antagonists to careful clinical testing and the resultant data to rigorous and objective analysis. Some of the results of this long term effort are presented here.

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CONTENTS

THE NIDA CLINICAL STUDIES

THE NIDA BEHAVIORAL STUDIES

CURRENT STATUS OF NALTREXONE SAFETY DATA

INTRODUCTION

Pierre F . Renault, M.D.

With the end of Phase II clinical testing of naltrexone in sight and the planning for Phase III underway, this seems an appropriate time to take stock, review our accomplishmerits, and re-evaluate our theories and preconceptions. Obviously, this cannot be done completely in only one volume. The full promise of naltrexone will only be realized after years of clinical innovation and careful observation. The purpose of this volume is to inform, act as a reference for clinical procedures, encourage interest and possibly stimulate further innovation and research with this important new drug.

The volume contains a series of five papers recounting the history of the political and bureaucratic processes necessary to have gotten us this far in the development of naltrexone. Dr. Julius gives a comprehensive statement of the interest of the Federal government in making a narcotic antagonist available for use in the treatment of chronic opioid dependence. Dr. Kaim details the decisions which led to the formation of the CENA committee and the National Academy of Sciences study. Dr. Tocus outlines the procedures that the Food and Drug Administration has developed to assure us of the safety and efficacy of all the drugs marketed in this country. This is a particularly helpful paper because it catalogs a process that most clinicians and scientists find bewildering. Braude and Morrison summarize the preclinical animal toxicity studies, a crucial and difficult step in the process of drug development. Dr. Hollister gives a candid portrayal of many underlying pressures that, fueledbysimplistic thinking and unrealistic expectation, complicated the beginning of naltrexone's development. Dr. Hollister's paper highlights a tension which is evident in other papers in this volume, a tension between the wish to respond to society's demand that a solution be found for the problem of heroin abuse and the wish to develop effective treatment for afflicted individuals without exposing volunteer subjects to undue risk. While it is true that political pressure was important in overcoming the inertia and getting naltrexone development underway, the pace of development has been in step with the pace of development of safety data and the requirements of the FDA. The paper by Dr. Willette on long-acting preparations points us toward the future. Many questions remain unanswered. What place will a sustained release preparation have in future treatment? Will it provide protection against the impulse with gradual extinction, or will it simply be another "sentence" removing responsibility from the patient and only delaying the eventual confrontation with heroin availability? How can these preparations be overridden when analgesia is necessary?

Although much of our primary concern has been the development of naltrexone as a clinically useful medication, the paper by Martin, et al, on the possible interaction of naltrexone with "naturally occurring morphine-like agonists"

indicates the importance of research on naltrexone in the development of knowledge about the basic processes of opioid action and physical dependence. "'Pure" antagonists have no known effect on normal organisms, but they may have important effects in organisms whose endogenous morphine-like substance (endorphin) system has been disequilibriated by chronic administration of opioid drugs. This possibility relates directly to Dr. Wikler's paper and his interest in a possible "satiating" effect of naltrexone in addicts. Later in the volume Thomas, et al, and Landsberg? et al, give clinical examples of such "satiation," and Goldstein supports the likelihood of this interaction.

In his paper Dr. Wikler continues his tradition of provocative theorizing about the addiction process and innovation in treatment methods. He reviews the concept of extinction which formed the basis for the use of narcotic antagonists in treatment. Convinced that extinction is the process which must occur for complete recovery from compulsive opioid use, Dr. Wikler suggests new ways of overcoming the failure of extinction to generalize beyond the therapeutic setting. Meyer, et al, have done extensive testing of the extinction theory under controlled conditions. They found that extinction achieved in a controlled inpatient setting did not generalize. Those patients who did well were those who continued to take their naltrexone after discharge and who made major lifestyle changes. This group of investigations has extended our understanding of human heroin taking by making systematic observations of heroin self-administration by individuals who did not know whether they were blocked by naltrexone or not blocked by placebo. It took longest for extinction to occur in those individuals with the longest history of heroin use. They have also demonstrated that interpersonal factors outweigh pharmacological factors in determining continued heroin use. They also advance the concept that taking naltrexone creates the "stimulus state" that signals heroin is "unavailable" and that therefore, addicts treated with naltrexone must eventually face the day when treatment ceases and heroin again becomes available. This concept resonates with the clinical concepts, later in the volume, of Lewis and Resnick, who feel that dropping out and returning to treatment are part of a process of gaining control over this state of facing heroin availability.

O'Brien, et al, review their procedures for outpatient extinction trials. Callahan, et al, while agreeing that change in lifestyle must be the ultimate goal of naltrexone treatment, find that naltrexone aids the cooperation of patients in their behavior therapy techniques aimed at lifestyle change.

Three investigators, Lewis, Resnick, et al, and Goldstein present clinical ideas on improving the efficacy of naltrexone. Lewis feels that a "permissive" attitude on the part of clinic staff is helpful in allowing patients to make full use of naltrexone. The goal of treatment is "internalization of control." Missing doses and clinic appointments can be seen as effortstointemalize the protection against the impulse to take heroin which naltrexone provides. Resnick, et al, in their followup study give data to support this "permissive" attitude by pointing out that subsequent treatment periods, after relapses, tend to increase in duration, that duration of naltrexone treatment is correlated with eventual success, and that a decision to take naltrexone is a "responsible" decision not to take heroin. They feel that the clinic staff must develop the trust of the client, so that he will transfer his reliance from drugs to his counselor.

Each of the investigators involved in the clinical trials of naltrexone was asked to summarize his experiences and to describe actual clinical procedures to provide a reference source of clinical experience for other investigators who plan to do clinical research with this drug. A wide variety of experience is represented in these papers. Among the participants in the NAS Cooperative Study, Parwatikar, et al, treated street addicts. Hurzeler, et al, and Curran, et al, treated primarily patients from the criminal justice system who were not currently physically dependent. Haas, et al, and Schoof, et al, inducted patients from methadone maintenance who required detoxification. Among the NIDA Clinical Study participants, Thomas, et al, have had the most extensive experience with naltrexone in a general clinic population. Greenstein, et al, have also treated a substantial number of patients and they give a very detailed description of the clinic procedures. Brahen, et al, also give details of a unique and important application of antagonist treatment within the criminal justice system.

All the clinical papers fulfilled our request for detailed information on clinic procedures. Their impressions and results are consonant on several issues:

1. Naltrexone is safe in the population tested, otherwise healthy male heroin addicts requesting treatment.
2. The major side effect is in the gastrointestinal system. The major symptoms are

anorexia, nausea and vomiting, and abdominal cramping.

3. They are unanimous in their agreement that naltrexone, at the equivalent of 50 mg/day, completely blocks euphoria and the development of physical dependence from street heroin.
4. The induction procedures currently employed are satisfactory.
5. The greatest problem with retention occurred during the detoxification process. Patients either could not complete detoxification or upon completion decided they did not need further medication.
6. The study itself, especially the double-blind study, was a factor in causing a low retention rate.
7. Retention in treatment is not an adequate measure of outcome.
8. Naltrexone is a drug for the highly motivated.
9. The goal of treatment should be focused on change of lifestyle.
10. The patient maintained on naltrexone must eventually face a crisis when he attempts to maintain control in the absence of naltrexone and heroin is again available.

Bradford has compiled an interim report on the combined safety data collected in 17 separate clinics involving 883 subjects who took study medication. Review of this data confirms clinical impressions presented earlier. There is no evidence of naltrexone being toxic. Specific symptoms: loss of appetite, nausea and vomiting, abdominal cramps and constipation did occur at a slightly higher frequency among naltrexone patients.

Broader questions also remain. Who are the patients likely to benefit from narcotic antagonist treatment? Are there any low-incidence side effects of naltrexone? Is naltrexone the "ideal" antagonist? Naltrexone was chosen because of its lack of agonistic properties, which in the case of cyclazocine were experienced as side effects; but would an antagonist with some reinforcing agonistic properties be more acceptable to patients and therefore effective in a larger propertion of patients? Does a pure antagonist such as naltrexone have a healing action on the disequilibriated "endorphin" system? What are the effects of naltrexone on protracted abstinence? Is naltrexone best viewed as a maintenance or a crisis drug?

It is our intent that this volume mark a point in time when we begin the final developmental phase. Our accomplishments consist of a body of thought and data on opioid dependence and strategies of intervention with naltrexone. Naltrexone is thus far safe and efficacious. Its usefulness is limited to a minority of patients characterized by their motivation. Perhaps naltrexone is not Dr. Hollister's "new magic bullet" for heroin addiction, but it has stimulated the imagination of researchers in this field and its promise seems to change and grow as our knowledge and understanding of basic processes increases.

The papers have been grouped roughly in the same fashion as they were presented at the National Academy of Science's Satellite Naltrexone Conference, held June 6 and 7, 1976, in Richmond, Virginia. The first set of papers describes the Federal role in the development of naltrexone. The second group of papers describes the conceptual basis and the results of the double-blind study of naltrexone's clinical safety and efficacy conducted by the National Academy of Science's Committee on the Evaluation of Narcotic Antagonists (CENA) . The third group of papers deals with the NIDA open clinical studies of naltrexone safety and efficacy. The fourth group of papers includes theoretical discussion and the clinical testing of behavioral hypotheses concerning the treatment of opiate addiction with narcotic antagonists. The last paper is a current assessment of the data collected on naltrexone safety to date.

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THE FEDERAL ROLE IN NALTREXONE DEVELOPMENT

NIDA'S NALTREXONE RESEARCH PROGRAM

Demetrios Julius, M.D.

The current naltrexone research program sup ported by the National Institute on Drug Abuse can be traced developmentally to its embryonic beginnings in the mid-1960's. At that time Dr. William Martin and his co-workers at the Addiction Research Center in Lexington, Kentucky initiated a series of studies into the use of narcotic antagonists for the treatment of opioid dependence (Martin et al. , 1966). The studies were a practical outgrowth of the theoretical formulations elaborated by Dr. Abraham Wikler over the preceding years (Wikler, 1948 and 1965). The results of the studies showed that a narcotic antagonist could be effectively used to block the euphorigenic and dependence-producing properties of opioids in man. Furthermore, this chemotherapeutic agent would produce neither physical dependence nor abuse liability in the treated individual. This was important because previous treatment drugs had the liability of producing their own degree of addiction.

These early clinical studies into the therapeutic use of narcotic antagonists might have faded into textbook obscurity had it not been for a number of concurrent social and political events that were rapidly developing. In the years following the tragedy of President Kennedy's assassination on November 22, 1963, our nation was quickly pulled into social turmoil at home and military turmoil abroad. By the late 1960's this multi-determined chaotic national scene had led hundreds of thousands of individuals to seek multiple avenues of relief. Many chose to seek refuge in what was felt to be the blissful escape provided by illicit drugs. This could be viewed sociologically as a massive attempt at self-medication. For many individuals, one dead-end to which these pharmacological avenues led was heroin addiction. Consequently by 1970 the use of heroin both at home and among our military personnel abroad had reached epidemic proportions. Among national authorities, apocalyptic visions of opioid-dependent armed United States soldiers, as well as similarly afflicted anti-war, anti-American anarchists roaming the streets looking for a "fix," provided necessary impetus to both the Executive and Legislative Branches of the Government to authorize funding for expanded research and treatment of opioid dependence.

On June 17, 1971, President Nixon signed into creation the Special Action Office for Drug Abuse Prevention (SAODAP), to coordinate the various resources of the cederal Government necessary to check the continuing spread of illicit drug abuse. These resources for drug abuse research, prevention, and treatment had been previously scattered across more than fourteen different agencies. In 1972, the Congress passed the Drug Abuse Office and Treatment Act which was signed into Public Law 92-255, Section 224, 86 statement 72 on March 21, 1972. Among the numerous provisions of the Law was a substantial financial support for the expansion of research on "long-lasting, non-addictive. blocking and antagonist drugs or

other pharmacological substances for the treatment of heroin addiction." With these substantial mandates, SAODAP's first director, Dr. Jerome Jaffe, set the development of a safe and effective narcotic antagonist as one of the highest priorities for this new agency.

THEORETICAL BASIS OF NARCOTIC ANTAGONIST THERAPY

Pharmacologically, a narcotic antagonist is a substance which has the ability to block the euphorigenic and dependence-producing properties of opioids (Martin, 1967). At the present time, it is theorized that this type of drug accomplishes this feat because of its structural similarity to narcotics themselves. Thus, antagonists have the ability to occupy the same presumed opiate receptor sites in the body as the narcotics do, and thereby produce competitive inhibition of narcotics. Different narcotic antagonist drugs also have differential abilities to produce both antagonistic and agonistic action. These differential properties are, of course, important in choosing the proper narcotic antagonist for this type of therapeutic use. It should be noted that a pure narcotic antagonist differs greatly from a drug such as disulfuram (Antabuse (R)) . When alcohol is ingested, by an individual taking the latter medication, a violent physical reaction ensues that can have life-threatening consequences. When heroin is injected in a dose which is blocked by the dose of the former medication being taken by an individual, no physical reaction ensues. Of course, an individual may attempt to overcome the blockade with too great an amount of heroin and fatally overdose himself.

This unique class of antagonist drugs thus formed the basis of a potential treatment modality as outlined by Wikler (1948, 1965) and Martin, et al. (1966). They postulated that operant conditioning plays an important role in initiating and perpetuating heroin use. Initially, the euphorigenic properties of narcotics probably act as strong reinforcers of what was conceptualized as "drug-seeking behavior" in the opioid-dependent individual. Thereafter, tolerance to the narcotic develops and slowly reduces the euphoric effects. In addition to the pursuit of pleasure (the euphoric effects), there is now within the individual a growing awareness of the need to avoid pain (the abstinence syndrome) . Therefore, the avoidance of the discomforting opiate abstinence syndrome also perpetuates the "drug-seeking behavior." Finally, a hypothesized "conditioned abstinence syndrome" may apparently be precipitated by environmental stimuli that have been associated with opiate dependence in the past. Occasionally after opiate detoxification, dependent individuals have described the onset of withdrawal symptoms by merely coming into contact with their previous environment. This conditioned abstinence syndrome may be characterized by increased reactivity to stimuli, prolonged abnormal autonomic responses, feelings of dysphoria, and often an intense "craving."

Quite logically, it was theorized, the narcotic antagonist could be used to control these various determinants of drug-seeking behavior. Since the antagonist would block the euphoria and the dependence produced by the opiates, the reinforcement for drug-seeking behavior provided by these two critical determinants of opioid dependence would gradually be attenuated. Furthermore, the antagonist would protect the detoxified individual against the conditioned abstinence syndrome. Thus, with the absence of these reinforcers would come the gradual extinction of the drug-seeking behavior itself.

The protection afforded by the antagonist would then give the needed time to aid the detoxified individual in altering his life's course. In the context of a close and humane psychotherapeutic milieu, the individual could learn to regain control over his own destiny. That is to say, he could begin to develop greater internal controls and greater independence and begin to extricate himself from the sticky external web of drugs and environmental pressures that had ruled his life until then.

DEVELOPMENT OF AN OPTIMAL NARCOTIC ANTAGONIST

In light of the above-described socio-political milieu and the enticing theoretical notions concerning the antagonists, we can easily understand why the development of a safe, effective antagonist was of the highest priority for SAODAP in 1971. SAODAP directors also recognized that the selection and development of such an antagonist was of no burning interest to the private pharmaceutical industry. The projected spending of research and development funds and time seemed to outweigh projected returns from what appeared to be a limited market. This projected spending was high because the development of a new drug is a complicated and time-consuming affair.

By law, any new drug must pass through rigorous and controlled testing in several animal species as well as in humans before it can be marketed. The testing is divided into a preclinical phase and three clinical phases. In the pre-clinical phase, the gamut of toxicity studies should be carried out on at least two different animal species. Provided the drug proves to have a sufficient margin of safety

in these toxicity studies, it may then be introduced into man for the purpose of gathering safety and efficacy data. Phase I of the clinical studies deals with the basic clinical pharmacology of the drug in man. This covers such areas as dosing levels, absorption rates, metabolites, and so on. Phase II represents limited and quite controlled clinical trials intended to demonstrate the safety and relative efficacy of the drug. For reliable results! it is desirable that these studies be carried out within a double-blind placebo design. That is, neither patient nor administering staff know which patients are on the drug and which on a placebo. Phase III then represents both controlled as well as uncontrolled clinical investigation in a much larger group of patients. The successful completion of this phase with a demonstration of drug efficacy is the final step before a New Drug Application (NDA) is submitted to the Food and Drug Administration (FDA). With approval of the NDA, the drug then is eligible for marketing to the general public, Of course, there is a constant financial risk involved in this process, for drug development may be halted at any point, based on unacceptable toxicity or disproven efficacy.

It was with this long and complex procedure ahead that the Federal Government, through the Special Action Office for Drug Abuse Prevention (SAODAP) and the Division of Narcotic Addiction and Drug Abuse (DNADA, NIMH), undertook the development of a safe, effective narcotic antagonist. A research plan was initiated by DNADA in September, 1971 to help organize such an efficient development. In this plan were outlined the necessary preclinical research, the procedures for clinical testing, and the cost and personnel estimates. Additionally the optimal characteristics of narcotic antagonists were described. These were as follows:

1. Ability to antagonize the euphoric high of opiates.
2. Absent or low-agonistic effects, especially unpleasant ones.
3. Does not cause physical dependence.
4. Does not exhibit increasing tolerance to its antagonistic actions.
5. Absence of serious side effects and toxicity even in chronic use.
6. Easily administered, i.e., no surgery or painful procedure involved.
7. Long-lasting or moderate duration of antagonist effects.
8. Absent or low abuse potential.
9. Reversible effects in case of medical emergency.
10. High potency to allow administration of small amounts in a biodegradable vehicle,
11. Easily available and inexpensive.
12. Therapeutic efficacy in treatment of narcotic addiction.

By early 1972 there were several antagonists in existence at various stages of development. The purest antagonist was naloxone. It seemed to be a potent antagonist and showed almost no agonist action of its own. Its main drawbacks as a therapeutic agent in opioid dependence were its high cost, the difficulty in synthesizing it, its very poor oral absorption rate, and especially its short duration of action in the body. Naloxone had been approved by the FDA for short-term use in humans as an antidote for opiate overdose. In spite of its drawbacks, naloxone had met with limited success as an adjunct to treatment by several investigators. This seemed encouraging for narcotic antagonist treatment in general.

Concurrently being developed was another promising and potent antagonist called cyclazocine (Jaffe, 1967; Resnick, et al., 1970 and 1971). This drug demonstrated a longer duration of action of up to 24 hours with 4 milligrams of the substance. However, its drawbacks were also recognized. These consisted of strong agonist properties when administered rapidly to individuals. These properties included quite unpleasant feelings described as dysphoria and psychotomimetic effects. Despite the tolerance that develops to these effects, cyclazocine was not well received by the addict volunteers and soon acquired a bad street reputation. However, it was successful in the treatment of some individuals, and these individuals are still, in fact, being treated with cyclazocine in certain clinics in New York City.

Additionally, three other compounds, designated as M-5050, BC-2605, and EN-1639A, wereinearly animal and human testing at the time. One of these, EN-1639A, seemed to be a potent antagonist and also did not show the dysphoric and unpleasant side effects of cyclazocine (Blumberg and Dayton, 1973). It had a good duration, in that 50 mg seemed able to block narcotic action for 24 hours. By late 1972, there was a substantial supply available for testing of this drug, which came to be known as naltrexone. By mid-1973 it became evident that this drug fulfilled the criteria of an optimal narcotic antagonist to a greater degree than any of the other available substances (Martin, et al., 1973a and 1973b; Resnick, et al., 1974a, 1974b, and 1974c).

Besides the research progress being made, there were also administrative changes occurring within the Government. In 1973, the Division on Narcotic Addiction and Drug Abuse

was separated out from NIGH and expanded into the National Institute on Drug Abuse. Thus, from 1973 to 1974, NIDA and SAODAP shared the responsibility for the ongoing development of the narcotic antagonists in general and of naltrexone in particular. By mid-1974, as SAODAP began to phase out of existence, the entire direction and monitoring of the naltrexone research program fell to the Division of Research, NIDA.

NIDA-SUPPORTED NALTREXONE RESEARCH

From 1973 to 1974, NIDA supported 26 various grants and contracts in pre-clinical and clinical studies directly related to narcotic antagonists. This support totalled over five million dollars. Approximately seventeen of these grants and contracts dealt with the use of naltrexone in clinical situations, and they fit together into a rather loosely knit naltrexone research program. Five of these research clinics were selected to participate in the double-blind placebo study of naltrexone that was, and still is, being conducted by the National Academy of Science (NAS). It was planned that such a study would satisfy in an elegant manner the Phase II requirements for new drug development and would demonstrate the safety and relative efficacy of naltrexone when compared to placebo. The five NAS clinics in the double-blind studv had a standardized group of three research protocols which they had to follow. The differences in the three protocols derived from the fact that each used a different type of opiate-dependent individual. The Baltimore and New Haven Clinics could use only "post-addicts" in their research. The Detroit and Sepulveda Clinics could use only "methadone maintenance addicts" And the St. Louis Clinic could use only "street addicts."

By contrast, the remainder of the grants and contracts consisted of a variety of controlled and uncontrolled clinical trials with naltrexone (Brahen, et. al., 1974; Brahen, 1975; Brahen, et al., 1976; Lewis, 1975; Meyer, et al., 1976; O'Brien, et al., 1975; Schecter, 1975; and Taintor, et al., 1975). Researchers in this group were free to use different protocols, to use different treatment settings, to treat different types of dependent individuals, and to pursue any variety of different research questions. This group of grants and contracts were called the NIDA clinics, for want of a better title. These NIDA clinics were later divided into a group of "open clinical naltrexone studies" and a group of "behavioral naltrexone studies," in an effort to bring greater order and specificity to the overall naltrexone program. In the former category were classed those studies which tested naltrexone within a variety of clinical contexts, whereas in the latter category were gathered those studies which specifically attempted to test out the original behavioral formulations discussed above.

All of the studies underway by 1974 were conceived by NIDA to represent Phase II testing of naltrexone. That is to say, naltrexone was receiving exposure in limited clinical populations. In Phase II, one of the chief responsibilities of NIDA was providing a watchful eye over the safety aspects of this drug when it was administered to humans. Consequently, a tight monitoring system had to be devised if the limited staff at NIDA was to function properly in detecting any ill effects of the drug. We therefore decided to establish the same kind of monitoring of all the NIDA research clinics that existed for the five clinics in the National Academy of Science's study. Biometric Research Institute (BRI) of Washington, D.C., was providing the monitoring and statistical capabilities for the NAS study and had developed a number of forms in conjunction with the NAS-CENA committee to carry this out. We therefore arranged for BRI to provide a similar monitoring function for the NIDA clinics. This consisted of gathering information on the monthly laboratory records (NAS-5a), monthly physical and psychiatric summaries (NAS-5b) , weekly symptom check lists (NAS-7), and the daily treatment records (NAS-9 and 9a) from the various open clinical and behavioral NIDA studies. Thus, by early 1975, we were able to gather a large quantity of both safety and efficacy information into the central data bank of Biometric Research Institute and were able to keep constant and close watch over any potentially unpleasant or harm ful effects of the drug.

Up to the present time, we have not seen any dysphoria or other psychic ill effects from naltrexone. The question arose in the past whether naltrexone caused an increase in blood pressure. According to the collective data, there seems to be a small (2-3 millimeters of mercury), but not statistically significant, rise in both systolic and diastolic pressure after initial administration of naltrexone. However, by four to six weeks, there is a return to baseline and in many cases a 2-3 millimeter decrease in both systolic and diastolic pressures (Brahen, et al., 1975; Resnick, personal communication). The only occasional side effect with some subjects seems to be an abdominal and gastrointestinal discomfort. When this was found at the beginning stages of treatment, it was attributed to minor withdrawal symptoms, because opiates were presumably still in the addict's system. However, these symptoms have been reported later on in treatment as well. Some researchers have found that these symptoms are some-

times relieved by antacids or by administering naltrexone to the addict after he has eaten. So it may be that naltrexone acts as a gastric irritant for some addicts.

An intriguing scientific question, however, is: what interaction could naltrexone be having with the endogenously occurring opiate-like compound that has recently been isolated by researchers? Could, in fact, these abdominal symptoms be related to such an interaction? If an individual who is being maintained on naltrexone has a quantity of this endogenous substance secreted into his system and it is, in fact, opioid in nature, is it not possible to assume that some of the same symptomatology might occur as if an external opiate were entering this individual's system in a sufficient amount to cause such physical effects? This symptomatology might therefore include minor withdrawal symptoms characterized by the abdominal discomfort described.

All of these minor side effects notwithstanding, we have seen no serious lasting side effects directly attributable to the ingestion of naltrexone. This antagonist appears to be a rather safe chemotherapeutic agent for the treatment of opioid dependence.

NALTREXONE PROGRAM-THE FUTURE

The NIDA naltrexone program currently consists of the NAS-CENA studies, the behavioral naltrexone studies, the open clinical naltrexone studies, and a number of studies at the NAS clinics which are essentially continuation studies of naltrexone safety and efficacy without the double-blind protocol. The NAS-CENA studies, which began intake in mid-1974, are now in the process of gathering follow-up data on the patients who have participated in the study. The double-blind has not yet been officially lifted for the investigators, and the existing data are now being tabulated and analyzed by BRI. These results will be forwarded to NAS-CENA committee which will issue its final report of this particular study by the end of 1976. Approximatelv 190 subjects have taken at least one dose of study medication, about half on placebo, half on naltrexone. The results are not in yet, but it seems that naltrexone was of benefit to a certain percentage of subjects in this study.

Aside from the NAS-CENA study, over 690 individuals have taken at least one dose of naltrexone in the other NIDA-sponsored clinics. This means that the total number of individuals who have at least one-time ingestion of the drug is therefore over 775. From a numbers standpoint, this would seem to be a more than adequate figure for satisfying Phase II requirements for clinical testing. We therefore consider the naltrexone program to be entering into the late stages of Phase II testing and are preparing the data collected to be submitted to the FDA by early 1977.

As this phase of naltrexone development winds down to conclusion before shifting into Phase III, so too does type and method of support provided by NIDA. The program began, as was described above, with an Executive and Legislative mandate for the development of a safe, effective antagonist. This mandate carried with it strong financial support in the form of contract monies. However, as Phase II winds down, so too do these contract funds. We have therefore increasingly encouraged interested researchers to seek grant support for proposed naltrexone research. So far, this seems to be working well, and basic clinical research continues with naltrexone.

As for Phase III of the drug's development, we are currently exploring the possibility that Endo Laboratories, a pharmaceutical firm and the owner of the patent for naltrexone, will be interested in carrying out that phase of ewanded controlled and uncontrolled clinical investigation. Although naltrexone safety seems to be well supported by the Phase II data, further monitoring of the safety will be carried out during Phase III, as well as the all-important testing of the efficacy claims for this drug.

Naltrexone has proved to be an interesting agent--almost a non-drug drug because of the lack of discernible effects other than its opiate-blocking capacity. This lack of other pharmacologic action may well prove to be one of the most attractive features of the drug. If the sentiment against the dependence-producing properties of other therapeutic modalities such as methadone and LAAM begins to expand, we may well be turning to a therapeutic program which includes naltrexone as a pivotal feature. This "anti-dependence" sentiment is current in two areas of the country, California and Massachusetts. Since these regions often herald what is to come for the rest of the country, we may find a receptive atmosphere for naltrexone as it is being prepared for expanded therapeutic use.

As it has been used to date, therefore, naltrexone seems to be a safe drug and an efficacious one in some addicts. However, further testing of its efficacy needs to be carried out in new and innovative techniques of administration. The question arises of how naltrexone's efficacy can best be maximized. Should we think of this drug as another long-term maintenance chemotherapy? Or would it be more effective when used in conjunction with short-term crisis-intervention techniques; or

in conjunction with various behavioral techniques; or in a contingency manner, so that the addict could ask to be put on naltrexone when he felt the need arise? Furthermore, the pre-clinical research into the use of implantable long-acting preparations continues unabated. These, however, raise-y ethical questions, besides questions concerning the efficacy of this mode of drug delivery. From another angle also, what factors such as attitudinal, environmental, and socio-cultural variables both in the clinic personnel and in the addicts treated are crucial for the effective use of this drug? Finally, are there intrapsychic or personality variables in addicts that make some appropriate for one kind of treatment and others appropriate for another kind of treatment? (Goldstein, 1975 and 1976; Martin, 1975; Willette, 1976).

The papers that follow in this monograph begin to touch on many of these intriguing research questions as well as describing with great clarity and detail many of the research discoveries and conclusions to date dealing with naltrexone as a therapeutic agent. It is our hope that further research will continue to reveal solutions to these questions, and we will be able to place naltrexone therapy most productively into the overall treatment approach to opioid dependence.

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REQUIREMENTS FOR DRUG DEVELOPMENT

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The development of a drug for marketiny is a topic which could constitute an entire series of lectures. During the next twenty minutes we will only be able to cover a limited part of the topic relating to drug development. Specifically, we will be concerned with those parts of the development of a drug relative to the regulations, and requirements of the Food and Drug Administration.

The Food and Drug Administration, or FDA, has the responsibility for seeing that drugs which appear in interstate commerce are both safe and effective for the claims for which they are being promoted and sold.

The Food, Drug, and Cosmetic Act in Section 505 says that no person shall introduce, or deliver, into interstate commerce any new drug unless approval of an application is on file with respect to that drug. It also says that any person may file with the Secretary an application for any drug which is intended for use in interstate commerce. This application must contain full reports of the scientific investigations which have been made to show whether or not the drug is safe as indicated and whether or not the drug is effective as indicated. It also must include a full list of the articles which are used as components of such a drug, a full statement of the composition of such a drug; also a full description of the methods used and the facilities and the controls used for the manufacture, the processing and the packing of such drugs. It must also contain samples of the drug and the articles used as components.

These are the items that are required in order to introduce a new drug into interstate commerce. Let's look for the remainder of our time at the requirement for full reports of investigations to show whether or not a drug is safe for use and effective for use.

These investigations are generally performed under the investigational new drug regulations, or the IND regulations. Such drugs may be shipped across state lines for purposes of study and they must bear the label

for investigational use only. It is necessary that the sponsor of an investigational drug demonstrate a pharmacologic effect of his product, either in an animal model or in an in vitro model before exposing humans to the drug.

There are exceptions to this policy, such as situations where the pharmacological effect is observed in humans who are receiving the drug for some other indication; it's possible there are other rare exceptions.

In addition to the pharmacologic effect in animals, it is necessary that the sponsor study the toxic effects of the drug in animals in order to determine whether any organs of the living organism may be irreversibly damaged because of the drug.

The design of the animal toxicity studies may vary with the type of drug under investigation. Generally, however, a determination of the median lethal dose, that is, LD_{50} dose, by several routes of administration in several species of animals is performed to estimate the lethal toxic potential of the drug. Thereafter, toxicity studies are performed on a multiple dose basis by the route proposed for clinical investigation. Animals from these studies are killed and their organs examined for possible toxic effects. For further use in man, chronic animal toxicity studies must be performed. These are done in at least two species, and the drug is given to animals for an extended period of time by the proposed route of administration in man.

For certain drugs, it may be necessary to do additional chronic toxicity studies to determine the carcinogenic potential of the drug in animals.

Before a drug is given to women of childbearing potential, reproduction studies are performed in animals. Segment 1 reproduction studies involve administering the drug prior to mating and determining the effects of the drug on reproductive performance. Segment 2 studies involve administering the drug to pregnant female animals during the period of gestation and determining the effects on the development of the fetus by performing cesarean sections and examining the fetuses for abnormal morphological effects. Segment 3 reproduction studies involve administering the drug prior to delivery and during lactation to determine the effects on the delivery process and on development of the young animal. Although such studies are performed, the safety in humans is only obtained through very cautious and careful observation of the human experience.

When sufficient animal toxicity studies have been performed, indicating it is safe to administer the drug to human volunteers and the chemistry of the drug has been delineated to the extent that the material proposed for human administration is well characterized chemically, then clinical studies may be performed initially in humans.

Clinical studies may be divided into three phases.

Phase I, Clinical Pharmacology is intended to include the initial introduction of a druq into man. It may be in the usual normal volunteer subjects to determine levels of tolerance, which will be followed by early dose-ranging studies for safety and in some cases early efficacy in patients. Alternatively, with some new drugs the initial introduction into man may, ethically or scientifically, more properly be done in selected patients. When normal volunteers are the initial recipients of a drug, the very early trials in patients which follow are also considered part of Phase I.

The number of subjects and patients in Phase I will, of course, vary with the drug but may generally be stated to be in the range of 20-80 on drug. Drug dynamic and'metabolic studies, in whichever stage of investigation they are performed, are considered to be Phase I clinical pharmacologic studies. While some. such as absorption studies, are performed in the early stages, others, such as efforts to identify metabolites, may not be performed until later in the investigations.

Phase II, Clinical Investigation is intended to include early controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on closely monitored patients of limited number and scope. Seldom will this phase go beyond the 100-200 patients on drug, all under rigidly controlled protocols.

Phase III, Clinical Trials are tne expanded controlled and uncontrolled trials. These are performed after effectiveness has been basically established, at least to a certain degree, and are intended to gather additional evidence of effectiveness, plus further evidence of safety, tolerance and definition of adverse effects.

The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations.

The plan or protocol for the study and the

report of the results of the effectiveness study must include the following:

1. A clear statement of the objectives of the study.

2. A method of selection of the subjects that (a) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

   (b) Assigns the subjects to test groups in such a way as to minimize bias.

   (c) Assures comparability of pertinent variables, such as age, sex, severity, or duratian of disease, and use of drugs other than the test drug in test and control groups.

3. Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjects response, and steps to minimize bias on the part of the subject and observer.

4. Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparisons are recognized:

   a. No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

   b. Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

   c. Active treatment control: An effective regimen of therapy may be used for comparison, e.g., wnere the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

   d. Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

5. A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

   a. For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to its identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

   b. Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

When results of all studies have been reported to the drug sponsor, analyzed, summarized and tabulated in an orderly and appropriate

manner, they are submitted in the form of a New Drug Application in support of a therapeutic claim. If the FDA concludes the submission presents evidence for the proposed condition, it is approved for interstate commerce. If the submission is lacking such evidence, it is declared non-approvable and the reason for the decision is given to the sponsor. If the deficiencies are corrected the application may be approvable and finally approved.

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PRECLINICAL TOXICITY STUDIES OF NALTREXONE

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INTRODUCTION

Toxicity studies of a new drug are carried out on animals prior to clinical trials. Acute and chronic toxicity studies can show whether observed toxic effects should preclude administration of the drug to man and can also alert the clinician to effects requiring particular attention. For these reasons the doses used are large enough so that some toxic effects will be produced, and will range upwards so that lethal doses can be determined.

Toxicity studies are designed to reveal the relation of toxic to effective doses. But the studies are not directly translatable to presumed effects in humans. The doses used in animals are much higher than expected clinical doses. The life spans of man and test animals are not comparable, so that, for example, there is usually a rapid increase in rodent mortality after 12 months or so and deaths during a second year of medication may be due to aging, the effects of the drug, or both. The Food and Drug Administration (FDA) guidelines suggest that at least one rodent and one non-rodent species undergo toxicity tests. In this case rats and monkeys were used.

PRECLINICAL TOXICITY STUDIES OF NALTREXONE

Naltrexone is a white crystalline solid, soluble in water, with a melting point of about 275°C. It is(-)-17-(cyclopropylmethyl)-4,5 aloha-enoxv-3.14-dehvdroxvmornhinan-6-one hyirochloride; (C_{20} H_{23} NO_4•HCl). Naltrexone was first investigated by Endo Laboratories for its acute toxicity in rats, guinea pigs and dogs. It was found to be relatively non-toxic acutely. In mice the intravenous (i.v.) LD_{50} was 180 ± 24 mg/kg, the subcutaneous (s.c.) LD_{50} was 570 ± 19 mg/kg and the oral LD_{50}, 1100 ± 96 mg/kg. In rats, the s.c. LD_{50} was 1930 ± 338 mg/kg and it was 1450 ± 265 mg/kg orally. In dogs, the s.c. LD_{50} was about 200 mg/kg and the oral lethal dose was approximated to be greater than 130 mg/kg. The acute oral toxicity study in dogs was confounded by the fact that the drug causes emesis.

In all of these studies the deaths occurred after tonic-clonic convulsions. This was usually preceded by restlessness, tremor, depression, salivation and/or retching and emesis. Peak effects were seen 30 to 60 minutes after s.c. administration. Signs of toxicity were usually gone after 2-4 hours and there was no delayed lethality.

In a series of studies carried out by Industrial Bio-Test under a NIDA contract, a small number (2 males and 2 females) of adult monkeys was given naltrexone in logarithmically increasing doses. By the s.c. route, some weight loss was seen at 100 mg/kg and prostration, convulsions and death were seen in 4 of 4 animals at 300 mg/kg. Naltrexone given orally in capsules produced hypoactivity, salivation and emesis at 1000 mg/kg and one of 4 animals convulsed and died at 3000 mg/kg.

SUBACUTE TOXICITY STUDIES IN RATS

Naltrexone was administered orally by gavage for 90 dose-days to 3 groups of 50 rats (25 males and 25 females) receiving 35, 70 and 560 mg/kg of body weight 6 days/week. An additional group of 25 animals served as controls and were dosed with distilled water. The dose levels in this experiment were approximately 35, 70 and 560 times the clinical dose of 1 mg/kg/day of naltrexone in humans. Except for salivation which occurred in the high dose animals during most of the study, and which became in part a conditioned response, the appearance and behavior of all the animals on test were essentially normal. Body weight gain and food consumption were comparable to control values, as were measured parameters in hematology and blood chemistry, with the possible exception of an unconfirmed elevated SGPT in one high level rat. Except for a slight increase in ketone in some of the high level animals. all urine analysis values examined were normal, Although some organs in the high level animals showed a slight trend toward increased absolute weight and percent of body weight, the changes are small and showed no definite dose relationship. There was no mortality that could be attributed to the drug, but one male rat in the high dose group was killed in an apparent dosing accident. All gross examinations at necropsy and subsequent microscopic examinations of fixed tissues were essentially normal. There were no findings of any significance that could be attributed to the action of the drug.

A 30 day subacute toxicity study by the s.c. route at doses of 3, 15 and 300 mg/kg showed similar results. There was no lethality and only at the high dose were mild excitation and conditioned salivation seen. High dose males had slightly subnormal weight gain but no hematological, pathological or clinical chemistry changes that could be attributed to the drug were seen.

SUBACUTE TOXICITY STUDIES IN DOGS

Naltrexone was administered orally by capsule for 90 days to 3 groups of dogs, consisting of 3 males and 3 females per group, receiving 20, 40 and 100 mg/kg of naltrexone 6 days/week. The high dose was originally 130 mg/kg but was reduced after a few days due to continued emesis. An additional group of 6 animals served as controls.

Appearance and behavior in most of the dogs throughout the dosing period were essentially normal. There was some evidence of slight depression in two dogs at the low dose and three dogs at the mid dose during the first few days of dosing, which subsequently disappeared. Tremor, salivation and emesis occurred in most dogs when the high dose of 130 mg/kg was given, but decreased markedly when the dose was decreased to 100 mg/kg. Conditioned salivation, emesis and intermittent slight depression and hind limb stiffness and tremor continued to occur, but with decreasing frequency as the study progressed. Physical, neurological and ophthalmological examinations, food consumption and weight gain were essentially normal. At termination, measured parameters in hematology, blood chemistry, urine analysis and physical and neurological examination were comparable between controls and experimental animals, and equivalent to pretest levels. Although there was a slight increase in a few absolute organ weights and/or percent of body weight ratios, these changes showed no dose relationship to the drug administration. The only gross findings present in a majority of the experimental animals and in two of the controls at necropsy were minor abnormalities in the lungs and congestion of the stomach and duodenum. Both of these are believed to be associated, at least in part, with the prolonged feeding of capsules, and with the salivation and emesis that occurred in many of the high level and a few of the mid level dogs. Histologically, the lungs showed evidence of mild to moderate chronic bronchitis and focal bronchial pneumonitis. The stomachs and duodenums were essentially normal. The mammary tissue from all the female animals on test, including the controls, showed varying degrees of duct and ductal proliferation and distention. A few cases of slight hyperplasia were also noted at both high and low levels. For the most part, the histological picture of the mammary tissue resembled a lactating breast , Sections of liver from a number of animals, both experimental and control, showed minor changes that included mild central phlebitis, focal necrotizing granulomas and congestion. Because roundworms were found in one dog, and eosinophilic granulomas

were noted in mesenteric lymph nodes from a number of dogs, the possibility exists that some of the changes in the liver were associated with a parasitic infection. In the opinion of the pathologist, none of the microscopic changes appeared to be drug-related.

A 30-day subacute toxicity study was also carried out in dogs, using the s.c. route, at doses of 2, 10 and 50 mg/kg given 6 days/week. At the high dose, mild toxic signs such as lacrimation, salivation, emesis, hind limb weakness and tremors were seen during the first week, but all signs gradually diminished and none were seen during the third week or at any time thereafter. No changes occurred in any clinical parameters or on physical and neurologic examination and no pathological lesions that could be attributed to the drug were found.

TERATOLOGY & REPRODUCTION STUDIES

Naltrexone was administered orally to rats at doses of 10, 30 and 100 mg/kg/day and to rabbits at 20, 60 and 200 mg/kg/day according to standard protocols for study of reproduction and teratology. These studies indicate that naltrexone had no effect on fertility and reproduction in rats and was not teratogenic in rats or rabbits.

TWO YEAR CHRONIC ORAL TOXICITY IN RATS

Study Design

This study was carried out under NIDA contract by Industrial Bio-Test Inc., in Northbrook. Illinois. It was begun on 9/6/73 according to the following dosing schedule:

Group	Dose	Males	Females
Control	0 mg/kg	90	90
T-I	10 mg/kg	90	90
T-II	30 mg/kg	90	90
T-III	100 mg/kg	90	90

Animals received these doses from the first day on the test.

Naltrexone was given by gavage in 0.1 to 0.2 ml distilled water. Rats were dosed at the same time each day seven days/week. Animals were housed individually and given *ad libitum* access to food and water. Ten animals of each sex per group were sacrificed after collection of urine and blood samples after 13 and 26 weeks of testing, and subject to a battery of hematologic, urinalysis and clinical blood chemistry tests. Gross and histopathologic examinations were also performed on all of these animals. At the 52, 78 and 104 week periods, fewer animals were sacrificed because of high mortality and gross and histopathology observations were made on some recently dead postmortem animals. Blood and urine samples were taken from 10 animals/sex/group through the 78th week and on 10 females/group, and on all surviving males at 104 weeks.

Mortality

The mortality data are presented in Figures 1 and 2, which show weekly cumulative deaths in each group. These figures do not include animals that were sacrificed or that were killed in dosing accidents. As can be seen, the spontaneous rate of mortality was rather high, so that at the end of the study the numbers of survivors were quite small. Among males, survivors were: 1 control, 2 in the 10 mg/kg group, 2 at 30 mg/kg and 2 at 100 mg/kg; among females the survivors numbered 14, 9, 14 and 5 in the same groups. At only a few points, however, are there statistically significant (Chi-square test) increases, and at some points decreases in mortality in any test group, and these differences are clearly not dose related.

Gross and histopathologic examination was conducted on tissues from representative animals that died from week 27 through the end of the treatment period. The cause of death in most animals examined was found to be inflammatory lesions of the respiratory system due to chronic murine pneumonia and acute bronchopneumonia which resulted in respiratory failure.

Reactions

Hyperirritability, expressed as shyness, resistance to handling and dosing and by some vocalization during dosing, was seen in some animals in all test groups. Hyperirritability was roughly dose related and became apparent at from 3 to 5 weeks. It was maximal from the 9th to the 12th week during which for males, 36% at 30 mg/kg and 95% at 100 mg/kg were affected and for females, 25% at 30 mg/kg and 95% at 100 mg/kg, were affected. Irritability declined to 5% or less by 20 weeks and remained there throughout the test period. The significance of these observations is somewhat obscure since no rieorous rating scale was used, and observations were made only once each week. At any rate, the effect was transient, indicating the possible development of tolerance.

Alopecia was seen in some test animals, beginning with 2.5% of females in the 100 mg/kg group at the 14th week and was maximal for this group in week 26, with about 20% affected.

FIGURE 1

NALTREXONE CHRONIC ORAL TOXICITY STUDY
MORTALITY OF MALE RATS (cumulated for each five week period)

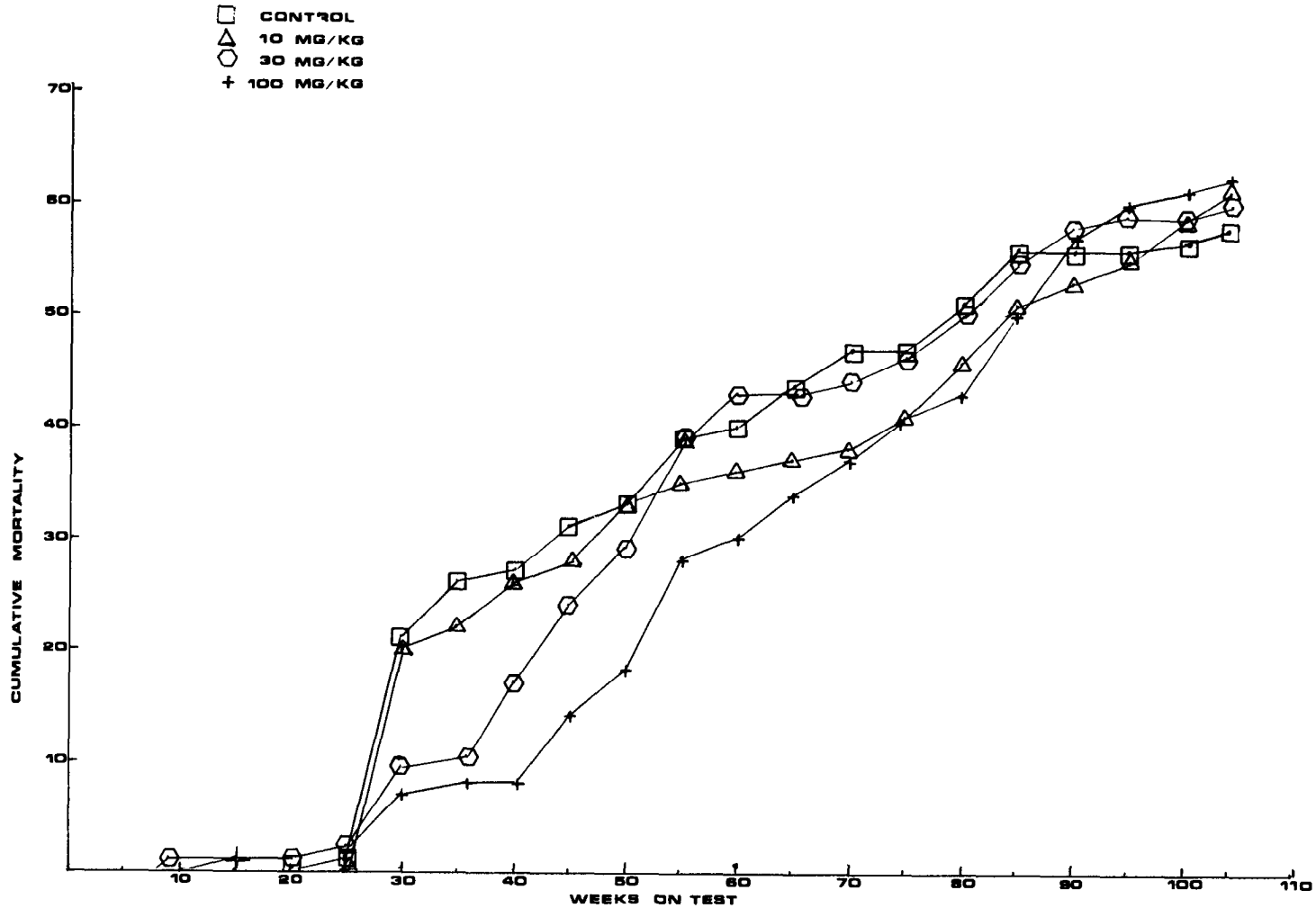
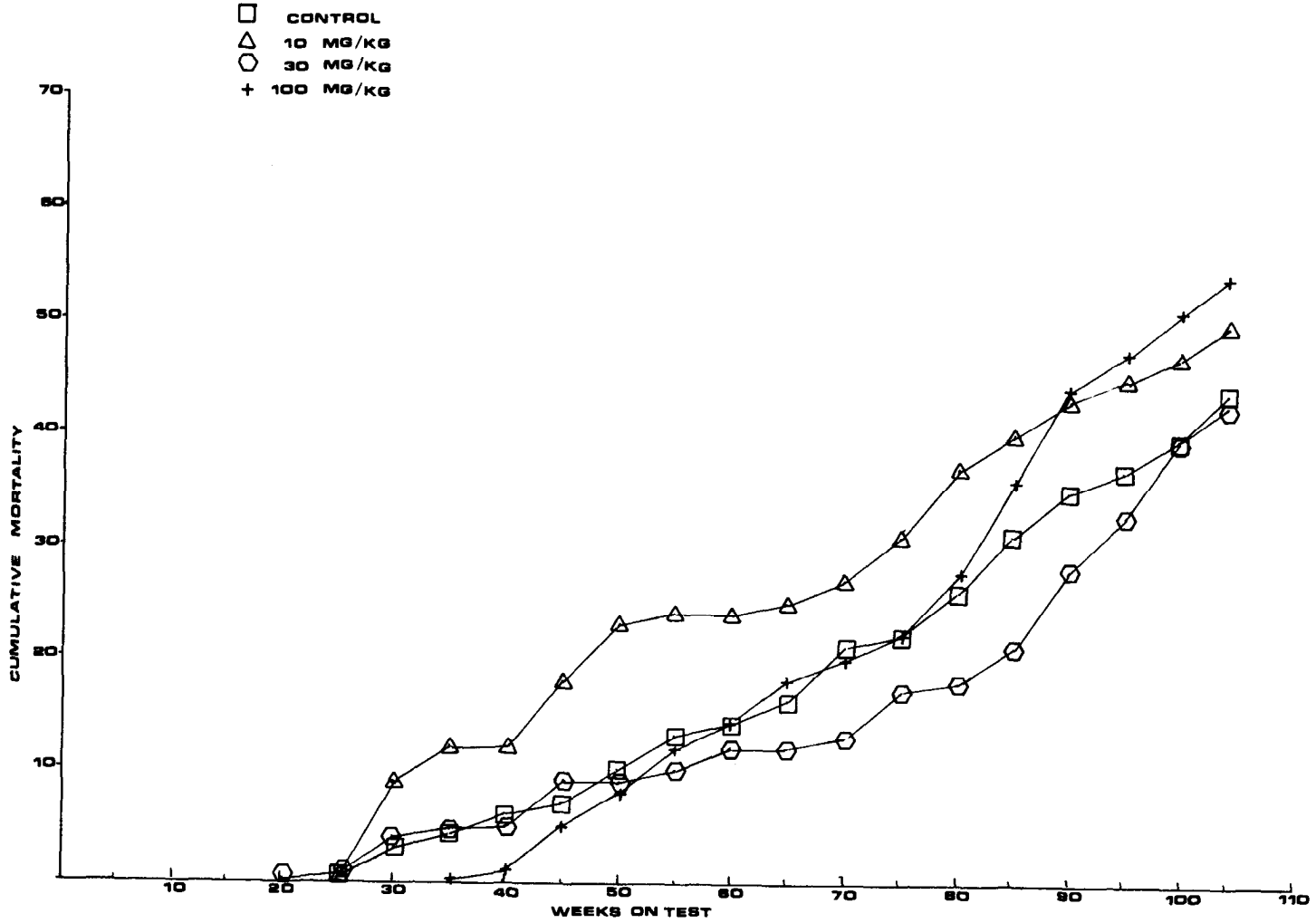


FIGURE 2

NALTREXONE CHRONIC ORAL TOXICITY STUDY
MORTALITY OF FEMALE RATS (cumulated for each five week period)



The females in the 30 mg/kg group had about 15% affected at week 26. The incidence of alopecia thereafter decreased to less than 5% in all groups from the 52nd week to the end of the test. Males had no significant loss of fur.

No other abnormal reactions were observed in any of the groups throughout the test.

Body Weight Gain

Mean body weights for each group are shown in Figures 3 and 4. These show that body weight gain among all test males were comparable to controls throughout the first 18 months of the test. The variations seen thereafter are not dose related and can be attributed to the small number of animals in each group, leading to a large change in mean values when a few animals die.

A depression in body weight gain in all the treated groups of females is evident from about 8 or 12 weeks to the conclusion of the test. There were no dose related differences among these treated groups, however, and the differences between treated groups and controls were rather small.

Total average food consumption was not different from control in any of the test groups.

Hematology, Clinical Chemistry and Urinalysis

The results of the hematologic studies showed statistically significant increases in prothrombin time for males in the 30 and 100 mg/kg groups at 52 and 104 weeks and in females in all test groups at 104 weeks. However, these values fall within the normal range for this parameter as measured in rats of this age and strain. The results in males, furthermore, are based on a small number of animals due to the high mortality. The results obtained in all other hematologic parameters throughout the study were within the normal range for rats of this strain, although some values were occasionally statistically different from control. Except for an elevated BUN in the few males surviving at 104 weeks, which was neither statistically significant nor dose related, results of clinical chemistry and urinalysis studies failed to show any values outside the normal range or any dose related effects.

Pathology

Gross and histopathologic observations of sacrificed rats or post mortem animals examined at each interval and at termination were similar for controls and test groups in all cases. Organ to body weight and organ to brain weight ratios were elevated in females in the 30 mg/kg and/or 100 mg/kg grouos for adrenals at 13 and 26 weeks. for liver at 26 and 52 weeks and for kidneys at 52 weeks. These changes were not in any case associated with gross or histopathologic changes,

Both sacrificed and postmortem animals showed lesions of chronic murine pneumonia. In some of these animals, there were concurrent inflammatory lesions in the lung consisting of a rather severe bronchopneumonia and pleuritis which were superimposed on pre-existing lesions of chronic murine pneumonia. Some animals had acute inflammatory lesions in other organs which were probably due to hematogenous dissemination of the infection from the lungs.

The cause of death in most animals that died on this test was attributed to inflammatory lesions of the respiratory tract due to this murine pneumonia.

Tumor findings were not different among test and control animals and were of types that are not unusual for a random population of adult albino rats of this strain.

Conclusion

No toxic signs that could be attributed to the test drug were found in this 2 year chronic oral toxicity study in rats dosed daily with 10, 30 or 100 mg/kg of naltrexone.

ONE YEAR CHRONIC ORAL TOXICITY STUDIES IN MONKEYS

Study Design

This study was carried out under a NIDA contract with Industrial Bio-Test, Northbrook, Illinois, and the performance site was their Decatur, Illinois laboratory. In order to determine the appropriate dose range for the one year study, a pilot study was undertaken. In this study, three large older adult (5-6.5 kg) female monkeys that had been in the laboratory for a long time, but which had been drug free for at least 8 months, were used. These animals were given naltrexone orally, by capsule, using a balling gun, according to the following schedule,

Test Day	Dose (mg/kg)
0-7	72
8-10	90
11-13	108
14-16	126
17-20	144
21-23	126

FIGURE 3

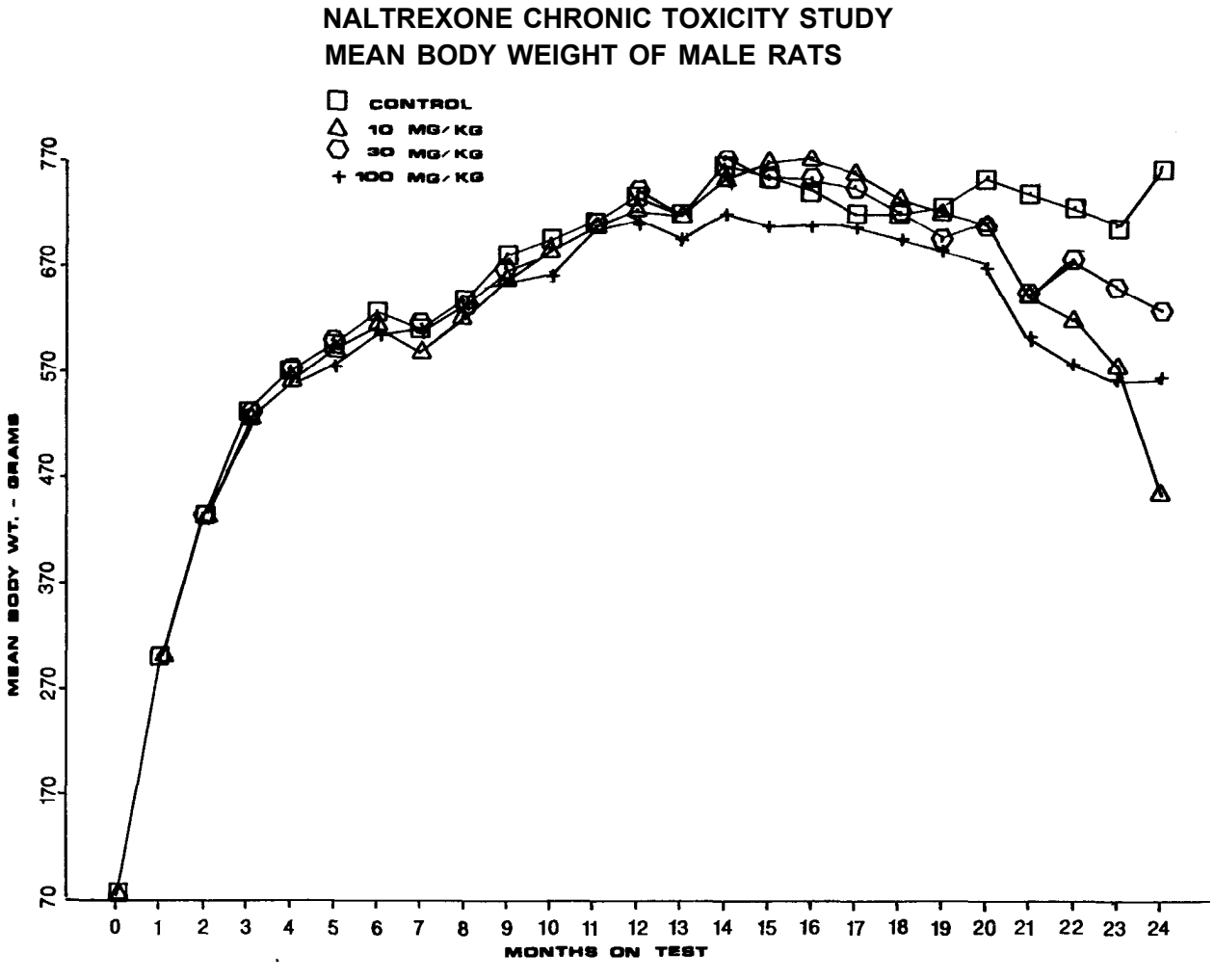
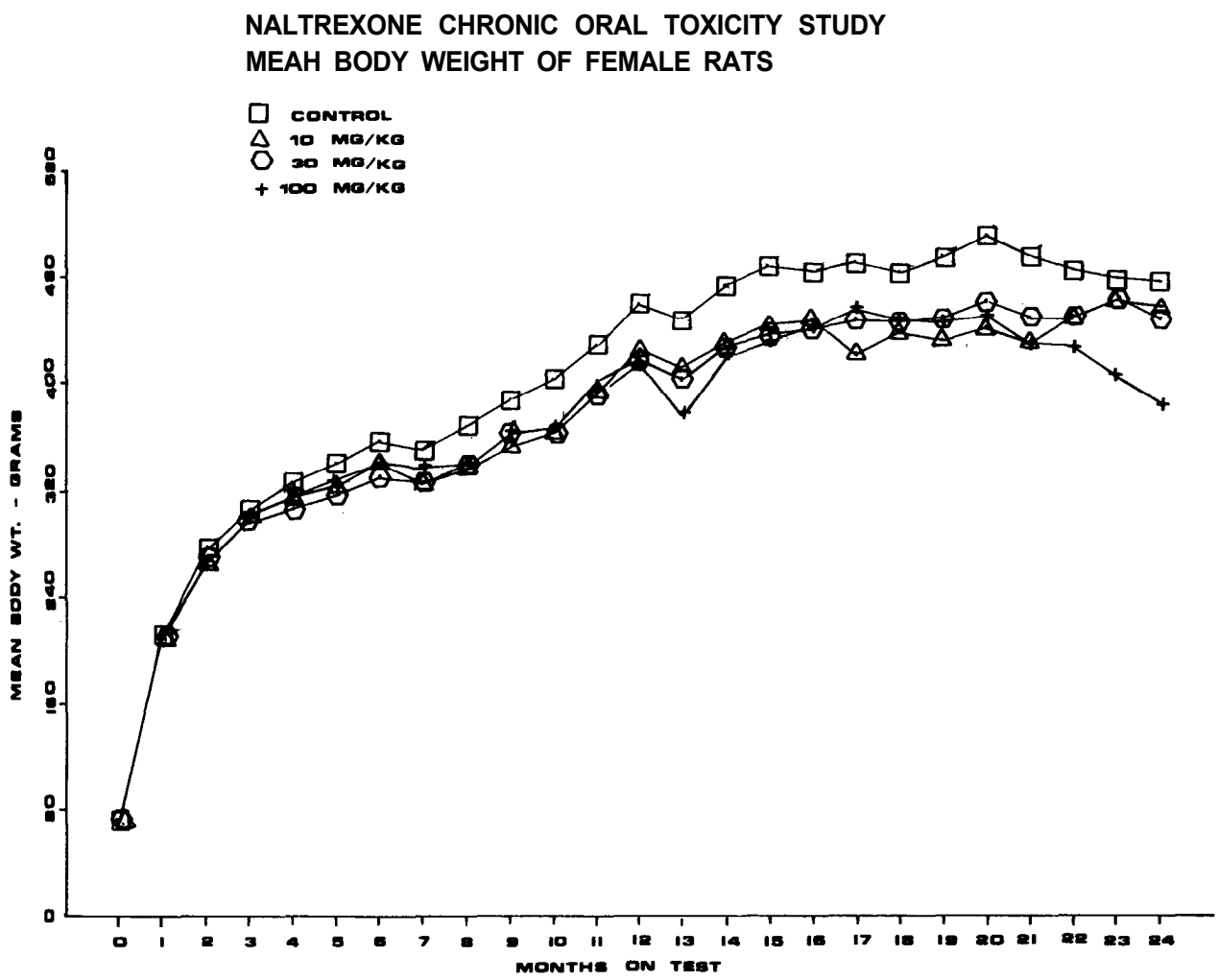

NALTREXONE CHRONIC TOXICITY STUDY
MEAN BODY WEIGHT OF MALE RATS
CONTROL
10 MG/KG
30 MG/KG
100 MG/KG
MEAN BODY WT. - GRAMS
770
670
570
470
370
270
170
70
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
MONTHS ON TEST

FIGURE 4


NALTREXONE CHRONIC ORAL TOXICITY STUDY
MEAH BODY WEIGHT OF FEMALE RATS
CONTROL
10 MG/KG
30 MG/KG
100 MG/KG
MEAN BODY WT. - GRAMS
0
80
160
240
320
400
480
560
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
MONTHS ON TEST

When the dose reached 144 mg/kg, there was a decrease in food intake which disappeared when the dose was reduced to 126 mg/kg. There were no other toxic signs in any of the three monkeys.

The animals used in the one year toxicity study were obtained from a primate importer who had held them for 8 weeks in quarantine to certify them free of serious diseases before release into this country. After these monkeys were obtained by the contractor, they were acclimated to his laboratory for 8 weeks and certified to be free of parasites and of tuberculosis. These young (3-4 kg) adult Rhesus monkeys could not be shown to be markedly different from those usually supplied and used in the contractor's toxicity studies.

In this study, monkeys were given naltrexone powder daily by capsule with a balling gun and controls were given a capsule, empty during the first few months of treatment, then filled with lactose powder. Animals were weighed and dosed at the same time of day and in the same order and observations of behavior and reactions were made daily 7 days/week.

The dosing schedule given is as follows:

Group	Dose	No. Males	No. Females
Control	0	8	8
T-I	6 mg/kg	8	8
T-II	12 mg/kg	8	8
T-III	24 mg/kg	8	8
T-IV	72 mg/kg	8	8

Note: The T-II group was begun three months after initiation of the study and gradually induced to the full 12 mg/kg dose in 3 mg/kg increments every two weeks beginning with 3 mg/kg. All other animals were begun immediately on the full dose of naltrexone.

Results

Toxic signs characterized as a "reaction syndrome" were observed in a total of 41 of the 80 animals on naltrexone. The occurrence of the "reaction syndrome" and of mortality is given in Table 1. This syndrome always had the same symptoms and sequalae with first an inappetence that resulted in a sharp decrease or halt in food consumption. This was followed by subsequent continuing weight loss throughout the course of the syndrome. The second sign, seen 2-3 days later, was mucoid rhinitis, and in a few cases, hemorrhagic colitis, which was often followed by other signs of respiratory infections including cervical lymphadenitis. Death followed in from 2 to 10 days after the first loss of appetite and occurred in all animals where the drug was not reduced or withdrawn.

As it was felt that it was essential to have some living monkeys at the end of a year for pathological analysis and in order to determine the limits of safety, it was decided that animals would be removed from the drug when they showed the reaction syndrome. These animals would then be allowed to recover and then be brought back to their original dose level by induction in 3 mg/kg increments at one-week intervals. In some of the sick animals the dose was reduced to a lower level and then brought back to the normal level after recovery. The whole 72 mg/kg group was removed from the study 18 days after dosing began, and the 24 mg/kg group was reduced to 18 mg/kg after 36 weeks on the study, and another group was added at 12 mg/kg. The 12 mg/kg group was induced to this dose from 3 mg/kg in 3 mg/kg increments at 2-week intervals.

The histopathological analysis of animals that died on this study gave no consistent drug related findings but did show both pneumonia and/or throat infections that could be related to dosing in 7 of 12 of these animals.

After the time (March 1974) that the reaction syndrome and deaths occurred and the study was redesigned, there were no further incidents of sickness in any of the animals on the study. One animal died as the result of a dosing accident just prior to sacrifice at 52 weeks. No withdrawal signs were seen when dosage was discontinued.

Hematology, clinical chemistry and urinalysis were performed at 0, 4, 13, 26, 39, 48 and 52 weeks of testing on surviving animals. The only change seen was an elevation of platelets for T-III females at 52 weeks, where all 3 survivors had counts of over one million. There were also no significant abnormalities found after ophthalmologic examinations or in blood pressure, EKG and respiratory rate measured at 0, 13 and 26 weeks of the study.

Gross and histopathological examination of all animals sacrificed at 26 and 52 weeks showed no evidence of drug-related pathological changes.

Conclusions

The results of this study are confounded by the reduction and stopping of dosing that occurred at the onset of the reaction syndrome. The study does show that it is possible

TABLE I

DOSE mg/kg	MALES		FEMALES	
	SYNDROME INCIDENCE (WEEKS ON TEST)	MORTALITY INCIDENCE (WEEKS ON TEST)	SYNDROME INCIDENCE (WEEKS ON TEST)	MORTALITY INCIDENCE (WEEKS ON TEST)
0	0/8	0/8	0/8	0/8
6	3/8;(1, 6-8) (4-7, 10-15) (1, 7-9)	0/8	7/8;(1) (1, 8-11, 13-15) (1, 4-6, 13-18) (2-4) (1-3) (2-8) (1, 11-15)	2/8;(18) (52 -probable dosing accident)
12	0/8	0/8	3/8;(2-6) (2-6) (8-12)	0/8
24/18	7/8;(1-4) (3-9) (11-15) (1-2, 8-died) (1-4, 12-13) (1-4) (1-4)	1/8;(8)	5/8;(2-3, 13-17) (12-13-died) (11-12-died) (11-12) (12-13-died)	3/8;(13) (12) (13)
72	8/8;all < 18 days	4/8;(2) (3) (3) (4)	8/8;all < 18 days	2/8; (3, 3)

Figures in parentheses indicate, for each individual animal, the weeks during which the reactions syndrome occurred; whether the animal died and the week of death.

to chronically administer 12 mg/kg with no adverse effects provided the dose is reached in gradual increments. No incidence of the raction syndrome occurred at 3 mg/kg but was seen with all higher doses. The reaction syndrome appeared to be associated with a loss of the normal defenses against infection, but whether this is a direct effect or is secondary to anorexia or other toxic effects causing the drop in food consumption, is not known.

SECOND ONE YEAR ORAL TOXICITY STUDY IN MONKEYS

Due to the confounding of the results of the one year toxicity study carried out at Industrial Bio-Test, another one year study in monkeys is now being carried out by Mason Research Institute.

Study Design

The study design is as follows:

Dose	Males	Females
0	5	5
1 mg/kg	5	5
5 mg/kg	5	5
10 mg/kg	5	5
20 mg/kg	5	5

Naltrexone is administered in distilled water with solutions adjusted so that 1 ml/kg is delivered using a Nelton catheter and each dose is followed by 4 ml of distilled water. During the first month of treatment, final drug doses were achieved in a step-wise manner by increasing the dose at weekly intervals from 1 to 5 to 10 to 20 mg/kg. The full dose was reached in August 1975 and treatment will be terminated in August 1976. One animal/sex/group was sacrificed at 6 months and one/sex/group will be observed for a 2 month recovery period. Animals are dosed daily seven days/week.

Results

In general, no consistent drug-related behavioral or physiological toxic signs have been seen except for a dose-related penile erection that occurred in the earlier weeks. General health, nutrient intake, all hematological and clinical chemistry parameters and urinalysis have been normal. The rates of growth have been intermittently slowed for some animals but are not related to dose or food intake. Bodv weight losses in the sixth month among females could not be definitively related to circulating drug levels because of meager data on the latter. In animals sacrificed at 6 months, no drug-related gross or histopathological cnanges were observed. Absolute and relative organ weights conformed to those of controls. No monkeys spontaneously died or exhibited morbidity during the study.

GENERAL CONCLUSIONS

From the studies reported here, it is evident that naltrexone is not toxic in any species at doses of at least 20 mg/kg, which is 20 times greater than the recommended clinical dose of 1 mg/kg. The data from rats and dogs would indicate than an even larger margin of safety is possible.

Based on these preclinical studies, the following parameters should be carefully monitored in clinical studies with this drug:

Anorexia
Irritability
Nausea and vomiting
Hematology and Blood Chemistry Parameters
Prothrombin time
Platelets
Blood Urea Nitrogen

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THE EFFECTS OF NALTREXONE IN THE CHRONIC SPINAL DOG AND ACUTE SPINAL CAT; POSSIBLE INTERACTION WITH NATURALLY-OCCURRING MORPHINE – LIKE AGONISTS

William Martin, M.D., James Bell, Ph.D., Paul Gilbert, Ph.D., Jewell Sloan, B.S., James Thompson

Over the last few years our work with the pharmacology of the narcotic antagonist has changed rapidly. Following our studies in which we demonstrated that the narcotic antagonists cyclazocine and nalorphine had agonistic actions and produced a type of physical dependence that differed from that produced by morphine, we postulated that they had agonistic actions at a nalorphine receptor, acting as either partial or strong agonists and were competitive antagonists at the morphine receptor (Martin et al., 1965; Martin and Gorodetzky, 1965; Martin, 1967). It was these observations that led us to the first practical application of the narcotic antagonists in the treatment of narcotic addiction because we had demonstrated: (1) Although tolerance developed to the agonistic actions of these drugs, it did not develop to their antagonistic actions, and (2) cyclazocine had a long duration of action when administered orally and parenterally in man.

We proposed that the antagonists might help those patients who wish to remain abstinent from becoming victims of their own impulsive drug-seeking behavior in times of stress, provide a circumstance whereby conditioned abstinence and drug-seeking behavior would be psychologically extinguished, and assist in the physiologic extinction of protracted abstinence (Martin et al., 1966; Martin and Corodetzky, 1967; Martin, 1968). It was our good fortune to study naloxone for its abuse potentiality and we found that it had neither agonistic actions of the morphine nor nalorphine type (Jasinski *et al.,* 1967).

In these studies we aiso explored the possible utility of naloxone as an alternative to cyclazocine for use in antagonist therapy but found its duration of action too short and its oral potency too small. This study, however, led to our investigation of the N-methylcyclopropyl congener of naloxone, naltrexone, as an orally

effective long-acting pure antagonist (Martin *et al.,* 1971, 1973). Naloxone, we thought, clearly decided the issue as to whether morphine was an agonist or not and favored viewing morphine as an agonist, a concept that had not been clearly articulated at that time (Martin, 1967). We also speculated about the possibility of the existence of a naturally occurring agonist and pointed out that the effects of nalorphine on the EEG, the ipsilateral extensor thrust and respiratory functions in certain species would be consistent with that formulation. Since naloxone did not produce hyperalgesia, pupillary dilation, respiratory stimulation or hypophoria in most preparations, we felt that there was no natural agonist involved in these functions. When Hughes (1975) first reported the existence of a polypeptide that shared actions with morphine on the guinea pig ileum in common with morphine, we again began to consider critically the problem of a natural agonist and recalled our experiments (McClane and Martin, 1967) in which we demonstrated that naloxone had a facilitatory action on the flexor reflex. This facilitation was thought to be "a nonspecific stimulant action" of naloxone and related to naloxone's convulsant action. Naltrexone also facilitates the flexor reflex of the chronic spinal dog (Martin *et al.,* in press).

Recent observations suggesting that there are three closely related receptors in the brain, the μ, κ and σ receptors, which are thought to be respectively responsible for the euphoric, sedative and hallucinatory effects of morphine- and nalorphine-like drugs, have led to a reformulation of the role of a morphine-related natural agonist in brain function. In recent studies, Dr. Bell has found that both naloxone and naltrexone facilitate both the C-fiber and a nociceptive ventral root reflex in the acute spinal cat. In contrast to earlier observations in the chronic spinal dog, this facilitatory effect increased with dose and was clearly apparent with minute doses of both naloxone and naltrexone. Further, Bell and Martin (in preparation) observed that nalorphine which is a partial agonist of the κ and σ type and a competitive antagonist of the μ type-also facilitated the C-fiber reflex in the acute spinal cat. In the chronic spinal dog, the predominant action of nalorphine is to depress the flexor reflex because of its κ agonistic effects. Bell and Martin (in preparation) confirmed the observations of Koll *et al.* (1963) showing that morphine depressed the C-fiber reflex. WIN 35,1972, a pure κ agonist that does not appear to occupy the morphine receptor, also depresses the C-fiber reflex. Naloxone and naltrexone antagonize the effects of both morphine and WIN 35,1972 but six times as much naloxone and naltrexone are needed to antagonize WIN 35,1972 as is necessary to antagonize morphine. These findings are similar to those of Kosterlitz et al. (1974) in the guinea pig ileum and to those made by Gilbert and Martin (in press) in the morphine- and cyclazocine-dependent animal. Cyclazocine is both a potent κ and σ agonist.

These latter observations clearly indicate that the spinal cord of the cat like that of the dog has both μ and κ receptors and that naloxone and naltrexone although acting as competitive antagonists at both receptors have a higher affinity for the μ than the κ receptor. The experiments with nalorphine would also argue that there is a naturally occurring μ agonist in the spinal cord. Considering that nalorphine is a partial agonist of the κ type, it must be further postulated that the level of μ tone in the spinal cord must be larger than nalorphine's κ depressant agonistic activity and when the μ depressant activity is antagonized by nalorphine, the resultant dysinhibition predominates. To explain the high potency of naloxone and naltrexone in facilitating the flexor reflex of the acute spinal cat but their relative inactivity in facilitating the flexor reflex of the chronic spinal dog, we have postulated that there are μ pathways descending from the brain stem that are inhibitory to the C-fiber and flexor reflex (Bell and Martin, in preparation). There are also intraspinal inhibitory κ neurones in the acute spinal cat. The descending inhibitory μ pathways must have considerable activity below the level of transection, hence accounting for the high potency of naloxone and naltrexone in facilitating these reflexes. In the chronic spinal dog, however, these descending pathways have presumably degenerated leaving only the intraspinal κ pathways which have a relatively low level of activity (see Figure 1).

It still remains to be demonstrated that naloxone and naltrexone have hypoalgesic effects in the intact animal and we must assume at this time that in all probability their activity in the awake rat, mouse and dog is quite low; however, if one assumes that one of the roles of the κ agonistic system in the dog is the production of sleep and the inhibition of certain types of convulsive activity, then the convulsant activity of naloxone and naltrexone and the sedative action of WIN 35,197-2 and ketocyclazocine can be readily explained.

As has been previously mentioned, the experiments of Gilbert and Martin (in press) strongly suggest that morphine is both a μ and κ agonist. We have thus initiated experiments to determine if we can identify the morphine

and the κ receptors *in vitro.* In homogenates of the brain which have been incubated with tritiated naloxone, morphine, levorphanol and WIN 35,197-2 prevent the binding of naloxone to receptor sites in rat brain homogenates. The inhibition of naloxone binding to these drugs is dose-related; however, a ceiling effect is encountered by all three drugs. The fact that WIN 35,197-2 does displace naloxone clearly indicates that there are κ receptors in the rat brain homogenates.

FIGURE 1

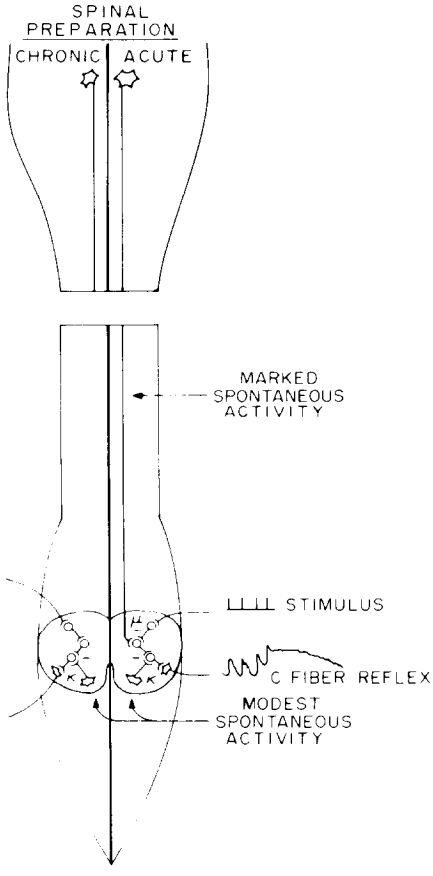

Figure 1. Hypothetical role of μ and κ agonists in spinal cord function.

The right half of this diagram illustrates the situation obtaining in the acute and the left side in the chronic spinal animal. Long axon neurones are illustrated arising in the brain stem and projecting down the spinal cord to a lumbosacral pathway. It is hypothesized that these long neurones liberate a μ agonist which is inhibitory to the flexor and C-fiber refflex. Also illustrated are intraspinal short axon neurones which are postulated to liberate a κ agonist which also is inhibitory to the flexor and C-fiber reflex.

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THE DEVELOPMENT OF SUSTAINED ACTION PREPARATIONS OF NARCOTIC ANTAGONISTS

Robert E. Willette, Ph.D.

INTRODUCTION

The use of narcotic antagonists in the treatment of opiate addiction is based on the concept of a pharmaceutical agent capable of blocking the reinforcing properties of a dose of opiate taken during an addicts rehabilitation. The rationale for use is that the antagonist blocks the opiate "high" and makes it pleasureless, thus removing the addict's incentive for continued use. Earlier successful therapy with cyclazocine and naloxone prompted the full-scale development of new and superior antagonists. Presently naltrexone is the drug under the most intensive clinical evaluation and appears to be a promising antagonist candidate.

It was felt from the outset that a most desirable component of antagonist therapy would be long-acting drug, so that the need for an addict to decide to take his medication would be minimized. Naltrexone in oral doses of 70 mg. will provide adequate blocking protection for at least 48 hours, or perhaps 72 hours in certain individuals. This is not felt to be a long enough interval between dosages to aid the addict in becoming dissociated from his drug-taking behavior .

It was recognized very early that in order to achieve the desired one week, one month or longer duration between dosages, it would be necessary to develop a long-acting drug delivery system or a sustained-release preparation of an acceptable but short-acting antagonist. A "drug-delivery system" is the unwieldy but currently favored expression describing any pharmaceutical preparation capable of providing a sustained or long-acting antagonistic effect. This effect may be achieved mechanically (e.g., by implanted discs with timed release capacity) or chemically (e.g., microcapsules, tubes, solid balls, gelatinous masses injected intramuscularly). Distinct from the problem not considered here, of finding an optimum antagonist, is the problem of inventing suitable carriers for the antagonist, releasing it uniformly bit by bit over a period of time.

Efforts to achieve satisfactory drug deliv-

ery systems were launched in the early 1970's by the City of New York Public Health Department and by the NIMH Division of Narcotic Addiction and Drug Abuse, now the National Institute on Drug Abuse (NIDA).

During this early period, the pioneering efforts of Dr. Seymour Yolles, University of Delaware, demonstrated for the first time that a sustained-release of an antagonist could be obtained from a biodegradable polymer, i.e., polylactic acid. This success generated expanded and intensified efforts, a summary of which is the topic of this article. At the present time, the program supported by NIDA includes six contracts that are concerned with the development of new delivery systems and three contracts that have the responsibility of evaluating them for potential clinical trials. The program is now narrowing down on those candidates that appear to have the best combination of essential properties to assure a successful clinical trial.

SYSTEM DESIGN SPECIFICATIONS

There are several properties and features that are important characteristics in the design and development of a clinically acceptable and useful delivery system. Some of these are:

1. Adequate and smooth drug release rate;
2. Ease of insertion or injection;
3. Consideration for the difficulty of removal by the patient versus the desirability of possible removal by the physician;
4. Biocompatability or lack of adverse tissue reaction or pain upon injection;
5. Ease and expense of manufacture;
6. Stability to sterilization;
7. Stability and storage characteristics;
8. Patient and physician acceptability.

Each of these considerations has a different relative importance and it is the task of the development team to select the optimal compromise of suitable specifications in order to bring a candidate preparation into clinical trial. It is recognized that the first trial preparation may not be the ideal system and that additional refinement may be necessary before a system could be introduced into wide clinical usage.

DEVELOPMENT PLAN

In the Spring of 1973, a new program for the development of a long-acting narcotic antagonist was initiated. It consisted of two contracts and two grants directed at the design and preparation of candidate delivery systems. Each group was also responsible for carrying out preliminary screening of the systems by in vitro and in vivo tests to select those that had the most promising release properties. This group included work on polylactide microcapsules, polylactide-polyglycolide beads, polyglyceride pellets and an insoluble salt complex, the later three having been originated under the earlier program supported by New York City.

In addition to these projects, three contracts were let to carryout in centrallized facilities the evaluation of all promising candidates emerging from the developers. These consist of a multiple level pharmacological and pharmacokinetic testing schedule as well as a range of toxicological measures. The overall scheme was designed in a pyrimidal fashion with more rigorous criteria required to pass from one level to the next.

At the heart of this plan was the recognition that an advisory group composed of scientists from several relevant areas was essential to assist in monitoring progress and making the difficult decisions about which leads to pursue. Their dedication and loyalty to the program has played a critical role in its success. The group has consisted of for more or less of the length of the program: Drs. Sidney Archer, William L. Dewey, James T. Doluisio. Fred A. Kincl. Fred Leonard. and James L. Olsen. Others, including Drs. Joseph Borzelleca, Douglas R. Flanagan, Stanley Kurtz, Grant Wilkinson and Ann Wolven, have also provided important input. Valuable advice and sharing of information has come from Drs. Gabrial Bialy and Henry Gablenick from the Center of Population Research, NICHHD, where a similar Program for long-acting antifertility agents is being supported.

At the present time the program has narrowed down to concentrate on four systems that have demonstrated the most promise. These will be described next.

CANDIDATE DELIVERY SYSTEMS

Polypeptide Tubes

Arthur D. Little, Inc.

In order to minimize the amount of animal testing required to receive FDA approval for an early clinical trial, it was felt desirable to select a system that is capable of being removed at the end of a month, but would eventually be able to be left implanted. A preparation that meets these and the other criteria is a tiny hollow tube of a synthetic polypeptide composed of a 35/65 copolymer of glutamic acid and leucine. Slowly biodegradable, these 2 mm by 10 to 20 mm tubes are filled with a solid core of naltrexone free base, which diffuses out through the tube wall. Rates of release may be adjusted by varying the wall thickness.

The tubes are manufactured in a fashion similar to candles, with a fine glass mandrel being dipped at a controlled rate into a heated solution of the polymer. The tubes are removed, filled with a little saline, a solid rod of 90% naltrexone bound in polymer, and sealed with a ca Sterilization is readily achieved with autoclaving.

Samples of these tubes have demonstrated up to 60 day sustained release. Current devices are releasing 10 to 30 micrograms of naltrexone per hour, which may be low for human needs. Devices capable of delivering higher amounts are being tested. Work on variations in polymer structure is being carried out in order to achieve a faster rate of biodegradation.

This work is under the general supervision of Mr. Kenneth Sidman.

Polylactic/glycolic Acid Beads
Dynatech Corporation

Potentially removable by a surgeon, these 1/16 inch beads of 90/10 polylactic and glycolic acid copolymer offer flexibility in dose administration. Implantable by means of a trocar, the 70% naltrexone free base loaded beads have shown continuous release for more than a month. Samples of beads have been periodically removed from injection sites and examined for biodegradation. They gradually soften, grow smaller or crumble, and eventually become undetectable.

Problems that remain to be overcome are sterilization, production scale-up and reproducibility of polymer synthesis. The latter still presents some difficulties because of the desire to produce polymers without metal catalysts.

This work has been directed by Dr. Donald Wise.

Polylactic Acid Microcapsules
Washington University

Two major advantages of a microcapsule approach to drug delivery is their potential for zero-order release rates and injectability. To date microcapsules of less than 180 microns of micronized particles of naltrexone pamoate coated with dl-polylactic acid have shown sustained release for more than forty days. They have been injected to date as a suspension in 2% aluminum monostearate gel in peanut oil. Other vehicles are being tried.

Additional work is still underway on perfecting capsules of naltrexone free base, which is more desirable as higher payloads of drug may be achieved and less toxicology would be required. A suitable sterilization procedure has not been worked out as yet. Several methods are being tested and advanced testing will be initiated as soon as these are ready.
These systems have been developed by Dr. Kurt Thies.

Naltrexone Aluminum Tannate
IITRI

Based on older formulation approaches, this insoluble aluminum tannate complex of naltrexone, when injected intramuscularly in a suspension of 2% aluminum monostearate peanut oil gel, gives a sustained release of over thirty days. The complex is readily prepared and easy to sterilize.

In preliminary studies on tissue compatibility, relatively little reaction was seen. It is known, however, that peanut oil suspensions are prone to cause occasional reactions. This preparation would require an extensive amount of toxicological testing in order to undergo human trials.

This preparation was developed by Dr. Allan Gray.

EVALUATION PROCEDURES

Preliminary Screening

Each developer was responsible for carrying out screening of trial preparations by in vivo and in vitro methods. The test used by all groups was the mouse tail flick method of Dewey and Harris. Animals were injected or implanted with the preparation and at various intervals, different groups were injected with morphine and their analgetic response measured for continued antagonism.

Some variations in in vitro tests were used, with the primary purpose of being to establish a correlation with the animal tests. Eventually, only the in vitro methods became necessary for general screening. As a follow-up to the animal testing, injection sites were examined for gross pathological reactions. Usually if nothing is observed by eye, little is found upon histology.

Advanced Pharmacological Evaluation

At Ohio State University under the direction of Dr. Richard Reuning, all candidate systems selected from preliminary screening were tested in the mouse tail flick test under standard conditions. Those systems showing unusual promise were then tested in rats using radiolabeled drug and the pharmacokinetics of release were studied.

In the course of developing suitable test procedures, considerable work was done on the metabolism and pharmacokinetics of naltrexone. This was essential for the calculation of actual release rates of the systems themselves.

Advanced Toxicological Evaluation

As candidate systems pass on through the pharmacological testing, they were evaluated in parallel at Industrial Bio-Test by Mr. Carmen Mastri. Depending on the dosage form being tested, the systems were implanted or injected into mice, rats and intramuscularly in rabbits. The last is the classical U.S.P. irritation test. When possible suitable positive and negative control materials were run concurrently.

Final Animal Evaluations

The most promising candidates eventually find there way into the most rigorous evaluation. The pharmacological test is carried out in monkeys that are trained to self-administer morphine. Developed at Parke, Davis and Company by Dr. Duncan McCarthy the suppression of morphine administration is an indication of how long the system delivers an effective level of naltrexone. At the same time, samples of plasma are obtained at various intervals and analyzed by the Ohio State group to determine the exact amount of drug released. Correlation of this data with pharmacokinetic measures of naltrexone in the same animals has given a thorough characterization of the candidate systems.

One of these candidates will soon be started in a detailed toxicological evaluation also at Parke-Davis. This will involve three species at three dose levels. Periodic sacrifices will be made to obtain a detailed pathological evaluation. The protocol will be designed so as to assure an early clinical trial based on the idea of removing the test system at the end of one month.

SUMMARY

After several years of tedious and often frustrating efforts, a few promising systems are now near final evaluation with the intention of conducting a human trial in the near future.

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THE NAS DOUBLE-BLIND STUDY

EVOLUTION OF THE NATIONAL ACADEMY OF SCIENCES STUDY OF NALTREXONE

Samuel C. Kaim, M.D

The 1972 legislation establishing the White House Special Action Office for Drug Abuse Prevention (SAODAP) contained a provision encouraging its Director to promote research programs to create, develop and test three classes of drugs:

1) non addictive synthetic analgesics to replace opium and its derivatives in medical use;

2) detoxification agents to ease the physical effects of withdrawal from heroin addiction; and

3) long-lasting, non addictive narcotic antagonists for treatment of heroin addiction.

In surveying the status of treatment modalities then in use for opiate addicts, SAODAP found methadone maintenance the most widely used and the most effective method for their management. However, it had a number of drawbacks, including:

1) it substitutes one addiction for another,

2) the side effects from the agonist properties of methadone,

3) the logistic problems in providing a daily treatment,

4) the dangerous diversion of methadone to the illicit market, and,

5) the negative image of methadone as a method of social control of minority groups.

As the above objections to methadone appeared to be mounting, SAODAP began a search for new approaches to treatment, concentrating largely on a pharmacologic approach involving opiate antagonists. It was felt that addicts willing to try this modality would become "immunized" to the rewarding effects of opiates, even-

tually being deconditioned to their use. The SAODAP was aware that antagonist therapy required cooperative, motivated subjects, so that it might be acceptable to a limited segment of the addict population.

However, as current treatments also appeared effective only for segments of the affected population, SAODAP felt it was worthwhile to explore any modality which appeared promising and offered certain advantages over the older methods. In fact, SAODAP considered a full exploration of the antagonist modality a matter of the utmost urgency. To expedite its study it was felt necessary to:

1) do it thru a nongovernmental agency (There are many constraints within government, including a ban at the time on the hiring of new employees.).

2) avoid the time lag of putting a contract to open bidding, such as would be required if the assistance of a university, research institution, pharmaceutical company or independent drug testing laboratory were solicited.

3) to seek a sole source contractor of such eminence that no auestion of propriety of the choice would be raised.

The SAODAP contacted the NAS/NRC Committee on Problems of Drug Dependence as a possible contractor, because:

1) the prestige of the NAS would assure the feasibility of a sole source contract;

2) the CPDD was the oldest body continually concerned with drug abuse and addiction (over 40 years of existence);

3) the CPDD had several members involved in the development and examination of opiate antagonists.

At the first meeting between SAODAP and the CPDD. Dr. Jerome Jaffe the first Director of SAODAP, suggesfed that a narcotic antagonist might have potential value in several clinical situations:

1) for addicts following withdrawal from methadone maintenance;

2) for addicts not interested in methadone maintenance treatment, and

3) for young or early users inappropriate for methadone maintenance treatment.

These potential clinical uses were based on use of an antagonist which would be essentially free of agonist qualities, and would be effective for at least 24 hours after a single oral dose. The SAODAP had previouslv initiated a major effort,' in collaboration with the pharmaceutical industry and the research community, to develop new opiate antagonists. Several compounds were in various stages of developmental testing: some had undergone toxicity testing in animals, others were still being so tested, some had already undergone Phase I testing in man, others were in early Phase II testing. In a preliminary effort to determine the efficacy of opiate antagonists, SAODAP had recently initiated a Phase II testing program in some ten clinics.

Dr. Philip Handler, President of the National Academy of Sciences, was then approached as to the feasibility of the Academy's involvement in this proposal. Dr. Handler expressed his own serious concern over the drug abuse problem, which was then much in the public eye, voicing a fear that extraordinary police measures minht ensue if it could not soon be demonstrated that drug abuse could be managed with some success by medical means. Although the Academy was usually averse to entering into "direct operations" of research projects, Dr. Handler felt that the urgency of the problem and the unique attributes of the Academy combined to dictate an exception be made. However, he felt that the huge effort required would be beyond the capacity of the CPDD, and suggested that a special arrangement be made for the large endeavor which would have to be mounted quickly. Subsequent negotiations between SAODAP and the Academy eventuated in a contract calling for establishment of a specially selected committee (with appropriate staff) within the NRC's Division of Medical Sciences to perform the following functions:

A. Recommend for testing, from among the candidate agents, those that should be used in clinical trials aimed at determing the efficacy of these agents in various clinical settings, and also recommend the various types of therapeutic programs and various types of patients in which the drugs should be tested.

B. Design:

1. Preliminary protocols;

2. Mechanisms and procedures for data collection; and

3. Criteria and mechanisms for evaluating the performance of the research and its products.

C. Develop guidelines for use in selecting clinics to participate in a pilot study, and assist and advise SAODAP in identifying the clinics and investigators suitable to the purpose of the study.

D. Receive comments, developed by invesitgators in clinics chosen by SAODAP to participate in the pilot study, concerning the protocols, criteria, mechanisms and procedures defined in "B" above and make appropriate revisions thereof.

E. On a periodic basis to be defined by the Committee, receive, analyze and evaluate progress reports made by the clinics participating in the pilot study , to assess appropriate adherence to and suitability of the protocols, mechanisms, criteria and procedures and to determine whether changes therein are desirable,

F. At an approprate time during the course of the pilot studies, appraise the results obtained and the procedures, mechanisms and criteria used. Develop recommendations and, if appropriate, revise protocols, etc., for full-scale clinical studies.

G. Advise and assist SAODAP in identifying the clinics and investigators suitable to the purpose of the full-scale study.

H. Receive, analyze and evaluate progress reports made by the clinics participating in the full-scale studies.

I. Receive and analyze reports on follow-up studies on patients who participated in the pilot and full-scale trials.

J. Prepare written reports as required by SAODAP and a final report at the completion of the study, evaluating the efficacy of the antagonists tested and identifying promising additional study approaches to the treatment or prevention of narcotic addiction.

The next step was the formation of the CENA Committee. The Chairman of the CPDD Committee, Dr. Leo Hollister, was asked to help nominate members from the CPDD to a small ad hoc Committee, which would later be augmented by appropriate additional members covering the disciplines which were relevant to the purposes of CENA. Four members of CPDD were then appointed to serve, under Dr. Hollister as Chairman. on the CENA Committee. Subsequently; four outside members (not from CPDD) were appointed, bringing the final number to nine.

NARCOTIC ANTAGONIST REVIEW

The SAODAP had previously discussed the development and testing of antagonists with several agencies, including the NIMH, the FDA, the DOD and the VA.

As Director of the Alcohol and Drug Dependence Service of the VA, I had discussed the potential usefulness of opiate antagonists with Dr. Jaffe and had surveyed the literature to attempt to determine which of the compounds might be the best choice for a large-scale multi-clinic study of safety, efficacy and acceptability.

Nalorphine had been earlier considered for clinical trial in the treatment of opiate dependence, but was felt to be impracticable for this use because of its short duration of action and the frequency of agonistic effects (Fink 1971).

CYCLAZOCINE

In 1959 cyclazocine, a benzomorphan derivative, was found to be an active analgesic which was effective in blocking the effects of opiates in stabilized addicts. In 1966 Jaffe and Brill and Martin et al. reported clinical trials with cyclazocine in the treatment of opiate dependence.

Although cyclazocine also had the agonistic side effects of opiates, it was shown to have a fairly long duration of narcotic antagonism, to be effective orally, and appeared to be an effective modality of treatment of opiate dependence.

Since those first trials, other investigators have reported varying degrees of success in this use of cyclazocine.

Martin and Sloan (1968) have reported that cyclazocine can produce analgesia, respiratory depression, miosis, constipation, sedation, irritability, "racing thoughts, "delusions and hallucinations. Tolerance develops to these effects, but not to its antagonistic properties.

They reported that slow induction on cyclazocine allowed tolerance to the side effects to develop. They started their six subjects with 0.1 mg orally b.i.d. and reached a final dose of 2 mg b.i.d. after a period of 13 to 33 days. At a 4 mg daily dose, it required 6 - 10 times as much narcotic to produce the same effects as it did in the same subjects when they were not receiving cyclazocine.

They also reported a mild abstinence syndrome when cyclazocine is withdrawn from subjects who have received it chronically. It did not lead to drug-seeking behavior. An early symptom of abstinence was found to be a feeling of lightheadedness characterized by patients as "electric shocks."

Jaffe and Brill (1966) started a cyclazocine trial with a small group of addicts who, roughly, fell into one of several categories:

1) subjects originally interested in receiving a narcotic as maintenance therapy;

2) patients who heard of cyclazocine from others, and were opposed to receiving methadone;

3) others who wish treatment and are willing to accept whatever is offered.

Their patients were admitted to a medical ward for physical examinations and laboratory studies. Those physically dependent on opiates were stabilized on methadone and then withdrawn over 3 to 6 days. Forty-eight hours after the last dose of methadone, patients were tested with 7 mg of nalorphine. If they had no discomfort, cyclazocine was started at a dose of 0.25 mg orally, 8 hours after the nalorphine. The total daily dose was (on average) increased by 0.25 mg every other day.

Side effects noted included: slowing of thinking, drowsiness, difficulty in focusing their eyes, masklike faces, episodes of depersonalization accompanied by anxiety and depression, insomnia, and occasionally an increased sense of energy. Tolerance developed to these effects.

Thirteen of 15 subjects stayed in treatment over the short period of several months at the time of the report. The patients were atypical: older, middle class, with little previous contact with the law, and with few previous attempts at hospital treatment. Group therapy was utilized, the patients forming a cohesive group and enthusiastically seeking to convert others to the new drug therapy.

In a subsequent paper, Brill, Jaffe and Laskowitz (1967) reported on the original 15 plus 72 new patients treated with cyclazocine. The average hospital stay was 2 weeks, followed by once weekly outpatient visits. Sixteen were still in treatment at the time of the second report and 5 who discontinued cyclazocine still maintained contact with the therapists. Most of these patients continued to use drugs, but on a more intermittent basis.

Ladewig (1971) reported on the treatment of 12 "motivated" opiate addicts with cyclazocine. Ten patients remained in treatment over one year. Seven of those 10 had no relapses, 3 returned to opiate use.

Petursson and Preble (1970) reported on the treatment of opiate addicts committed to the Manhattan State Hospital Drug Addiction Unit for 9 months of inpatient plus 27 months of outpatient treatment. Sixty-two male addicts were treated with cyclazocine: 53 achieved a maintenance dose of 8 mg daily, 9 reached a 12 mg dose level.

Thirty-six of these patients completed the inpatient program; 13 eloped from the hospital; 11 eloped from after-care. Seventy-five percent of these addicts had been labeled personality disorders. The authors considered cyclazocine treatment effective in the "motivated" cases.

Resnick, Fink and Freedman (1971) reported two series of male addicts treated with cyclazocine in a special unit at the Metropolitan Hospital Mental Health Center. Patients were primary opiate addicts, over 18 years of age, and voluntary.

Patients were offered the choice of detoxification only, methadone maintenance or cyclazocine. Induction to cyclazocine started with 1 mg daily, increasing to 4 mg daily after an average of 4 days. Naloxone was available to patients on request, during induction, as an antidote to the side effects of cyclazocine.

Cyclazocine was dispensed at the Clinic or by a responsible person living with the patient. Of 62 patients, 60 completed the 4-day induction; 38 requested naloxone during induction, 3 beyond induction (up to 14 days).

Twenty-one patients from an earlier study, who had been receiving cyclazocine 1-4 years, were all working or in school. Four patients who discontinued cyclazozine at their own request, had not been re-addicted. Six patients dropped out after 7 months to 3 1/2 years on cyclazocine.

In a subsequent study, 59 patients who requested cyclazocine were inducted to the drug. (In the previous study patients merely had to accept cyclazocine.) Twenty-two of the new group dropped out of the trial. Marital status and work or school attendance were significant prognostic factors.

NALOXONE

N-ally1 noroxymorphone hydrochloride (Naloxone) was reported by Blumberg et al. (1961) to have narcotic antagonist properties. Jasinski et al. (1967) found naloxone five to eight times as potent as nalorphine in precipitating abstinence in morphine dependent subjects. In contrast to nalorphine and cyclazocine, naloxone was found not to produce physical dependence, nor to have significant agonistic activity. As in the cases of nalorphine and cyclazocine, tolerance to the antagonistic property of naloxone does not develop during chronic administration.

Zaks et al. (1969) felt that its relative absence of agonistic activity and side effects would make naloxone prefer able to cyclazocine in the long term treatment of opiate dependence. They found a daily oral dose of 200 mg afforded six hour protection against a challenge of 25 mg of heroin. 400 mg of naloxone afforded blockade of 50 mg of heroin for 6 hours. 800 to 1250 mg of naloxone was necessary to protect against 50 mg of heroin for 18 hours. These authors were unable to achieve 24 hour blockade with 1500 mg of naloxone.

Kurland et al. (1973) reported a double blind study of the use of naloxone in 119 male addict parolees over a period of 9 months. Subjects were randomly assigned to one of three groups: a) concurrent controls were assigned to a weekly program of group psychotherapy and urine monitoring; b) the naloxone group received the drug on a fiexible dosage schedule of 200 - 800 mg daily, depending on the results of the urine tests; c) the third group received only placebo pills ranging in number from two to eight daily depending on the results of the urine monitoring. All three groups participated in the weekly group psychotherapy program.

Only 25% of the control group completed the program, contrasted with 44% of the naloxone group and 51% of the placebo group. The naloxone group performed better in respect to incidence of positive urines: 11% vs. 30% for the placebo group.

The authors speculate that these results may reflect a negative relationship between effectiveness and acceptability of naloxone in these addict parolees: the less motivated placebo subject may have realized he could experience his customary “high” and still remain marginally involved in the program, while the less motivated naloxone subject may have left the program when he no longer obtained gratification from narcotic drug taking behavior.

NALTREXONE

Naltrexone Hcl was synthesized by Blumberg, Pachter and Matossian of Endo Laboratories (1972). It is derived by substitution of a cyclopropylmethyl group for the methyl group on the nitrogen atom of oxymorphone, a narcotic analgesic. It is thus chemically related to naloxone, an almost pure narcotic antagonist.

Naltrexone shows slight agonist activity in animals. It is a very potent antagonist in animals, about 8 times as active (orally) as naloxone, and longer acting.

Naltrexone has had acute, subacute

and 90-day toxicity studies in animals. With oral administration, it produces only mild toxic effects at 100 mg/kg/day, which is 30 times the probable maximum clinical dose of 200/mg/60 kg/day.

Martin, Jasinski and Mansky (1971) tested naltrexone in volunteering prisoner post-addicts. On oral administration, most subjects reported no symptoms, excepting two who became sleepy. Diastolic blood pres - sure increased slightly, body temperature decreased slightly, pupils were slightly constricted.

The Lexington group found 50 mg of naltrexone orally produced a level of narcotic antagonism comparable to that produced by 4 mg of cyclazocine. There were no withdrawal symptoms when naltrexone was discontinued after chronic oral administration at either the 30 or 50 mg daily dose level.

The authors felt that naltrexone has definite advantages over naloxone because of its greater potency and longer duration of effectiveness. They also felt that naltrexone had the advantage over cyclazocine in its relative lack of agonis tic effects.

Resnick et a1.(1973) studied the use of naltrexone in 37 addict patients during the period of January through April 1973. Some of these subjects volunteered for this experimental treatment following a period on a methadone maintenance program.

The patients were first detoxified from opiates and received a complete physical examination, chest x-ray, SMA-6, SMA-12, CBC, reticulocyte count, platelet count, ESR and urinalysis. These exams were repeated prior to discharge from the hos pital. The subjects were then maintained on naltrexone at daily dosages of 120 to 200 mg.

Naltrexone was administered as a single daily oral dose. Initial subjects started at 20 mg/daily. This starting dose was later increased to 30, 40 and 50 mg/day. Daily dose increments were 10 mg/day and later 20 mg/day.

Thirteen of the 37 patients reported symptoms during the first 2 days on naltrexone: some felt tired or sluggish, nervous or irritable, some had difficulty falling asleep. These side effects were mild or moderate, subsiding within a few days, usually despite further increments in dose. No subject reported these symptoms following stabilization on a fixed daily dose. The authors felt that these symptoms resulted from precipitated abstinence.

After the first four days of naltrexone induction, 22 of 34 patients experienced no symptoms during the period of increasing doses to the 1.26 to 200 mg daily level. There was no consistent difference in the incidence or intensity of symptoms which appeared at 20 mg/day increments compared with 10 mg/day increments.

Five patients complained of intermittent crampy abdominal pain, sometimes associated with mild nausea. Headache was a fairly common transient symptom. Most of these symptoms subsided spontaneously or were relieved by diazepam 10-20 mg daily.

Blood pressure was not significantly changed, but there was a trend toward narrowed pulse pressure. Heart rate and temperature fluctuated unrelated to naltrexone dosage. No significant changes were noted in laboratory determinations.

Eight of 10 subjects abruptly withdrawn from 200 mg/day naltrexone experienced no abstinence effects. One subject complained of headaches, fatigue and malaise; another had chills and abdominal pains on the first withdrawal day.

Twenty-seven subjects were challenged with 25 mg heroin i.v. Three of three had complete blockade 24 hours after 50 mg oral naltrexone. Six of six experienced complete blockage 48 hours after 120 mg oral naltrexone. Four of nine reported blockade 72 hours after a dose of 200 mg naltrexone. One subject required 200 mg/day naltrexone to achieve complete blockade at 24 hours.

Three patients discontinued naltrexone before completing induction on the drug, but one of these continued treatment without medication. Of 20 patients discharged to the outpatient clinic, 17 continued on the program, receiving naltrexone daily, the medication being dispensed for self-administration on weekends.

The authors found naltrexone to fulfill the criteria for clinical usefulness in treating opiate dependence: a) oral effectiveness, b) non addicting, c) providing blockage to heroin for 24 hours or more following a single dose.

SUBSEQUENT PROGRESS

After retiring from the VA and subsequently joining the NRC as Director of the CENA staff, I circulated my literature survey among the members of the CENA Committee.

Although other newer opiate antagonists were becoming available (e.g. BC 2605. M5050), none had reached a stage'of study which would have permitted large scale human studies in the near future.

Of the three chief contenders, naltrexone appeared the closest to fulfilling the criteria for an antagonist suitable for use as part of a long-term regimen for the treatment of opiate addicts:

1) it is orally effective for 24-72 hours, depending on dose;

2) it is not addicting;

3) it appeared to be relatively non-toxic, and

4) its side effects were fairly minor and well tolerated.

In contrast, cyclazocine had many disagreeable agonistic effects and naloxone has a short duration of action, even in large doses.

The difficulty with naltrexone lay in its rather short history of human trials. However, animal and human studies were still under way. The Committee decided that if the latter should prove the drug safe for chronic administration, naltrexone would be selected for the study.

At the first meeting of the Committee, September 21, 1973, the Chairman appointed a Subcommittee to decide on preliminary protocols for the CENA pilot studies. and another subcommittee to develop the instruments necessary for the purpose of the studies. Dr. Hollister also stressed the need to select the clinics for participation in the studies on the basis of good medical and laboratory support and staff oriented toward evaluating results.

At the February 1974 Committee meeting it was decided to pretest the proposed measurement instruments in six VA Hospitals, and also to survey prospective study clinics as to availability of appropriate subjects and as to attitudes of staff and patients toward withdrawal from methadone maintenance and toward use of a narcotic antagonist.

Following several meetings of the subcommittees, measurement instruments and three study protocols were adopted by the full committee.

Clinics which met the committee's criteria were site visited by CENA staff, and then selected to participate in the studies, one assigned to the "street addict", two to the "post-addict" and the remaining two to the methadone maintenance protocol: NAS. with the authorization of SAODAP. entered into subcontracts with Educational Testing Service for standardization of the instruments, and with Biometric Research Institute for collection, collation and analysis of the data to be gathered in the trials. Training visits were then made by staff of CENA and BRI to the five participating clinics and to two VA hospitals which agreed to complete sets of study forms for use by ETS in its standardization effort.

The PHS pharmacy in Perry Point, Maryland, which had prepared the study medication, released it in mid-1974 and the clinics began to process subjects for entrance into the trials.

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PHILOSOPHY AND STATUS OF NAS CENA STUDY

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Narcotic antagonists as potential treatments for opiate addiction provided a classic example of how medical science often gets involved in politics. Despite some indication of a temporary decrease in the rate of addiction in the United States, political pressures were still high in 1973 to "do something" about the opiate problem. Narcotic antagonists seemed, at least to the politicians, as a new magic bullet which might quickly and cheaply solve the problem. What could be simpler than to block completely the action of narcotics and thus make their use unrewarding? And what could be simpler than allocating a great deal of money to get these magic bullets into the patients?

So great was the rush that ordinary administrative procedures were not considered adequate. One could not take time to await grant applications for the study of narcotic antagonists, nor even to solicit ordinary contracts. A contractor of such high scientific esteem had to be obtained which would qualify as a "sole source" so that studies could be started right away. The National Academy of Sciences, through its Committee on Problems of Drug Dependence (CPDD), was a natural contractor. Accordingly, the first overture from the Special Action Office for Drug Abuse Prevention (SAODAP) was to the NAS Committee on Problems of Drug Dependence.

For reasons still not entirely clear, the internal administration of the NAS decided that the CPDD was not the proper vehicle for doing this study, but rather that a special committee, the Committee on Evaluation of Narcotic Antagonists (CENA), be set up. The chairman of CENA was also the chairman of the CPDD and several members were recruited from CPDD, but administratively the committees were separate. Additional members were recruited from outstanding people in fields not heavily represented on the CPDD, but thought to be useful for doing an evaluative study.

During the preliminary negotiations, a fire line had to be drawn between 'operational" and "advisory" functions. The NAS was quite sticky about its role only as an advisor and did not want to run the study. To some extent, this attitude frustrated the hope of SAODAP that the CENA might operate as a true sole source contractor. CENA did, in fact, become an advisory committee and SAODAP was forced to contract with those clinics selected to do the study. The contract was signed on the very last day of the fiscal year in which the money had been appropriated, a situation not too uncommon in the government.

With its role clearly delimited, the task of the CENA was to select the drug or drugs to be studied, to advise on the suitability of the clinics proposed for the study, to devise an experimental protocol and data collection procedure, to oversee the independent contractor doing the statistical handling of the data, and to prepare a summary report of the study when it was completed, All this was to be done in three years.

The major task of CENA was the preparation of the protocol and the data collection procedure. We decided that a controlled comparison of the narcotic antagonist, in this case naltrexone, was to be made against a placebo. This decision was made because we felt that one should at least try to ascertain the feasibility of doing such a study, none ever having been done with methadone. Some of our wildest hopes were that such a study would not only be feasible but also that it might provide some preliminary support for the efficacy of naltrexone. Another reason for using the placebo control was that it would provide a control against questions of toxicity to the drug, whether these be clinical side effects or abnormal laboratory values.

In devising the data collection procedure, we made the Universal error in any such large-scale formal study, especially of a new drug or a new area of clinical research. We collected far more data than we could possibly use, and much that in retrospect proved to be useless. Inefficiency of this sort is unavoidable, and probably necessary, as it provides a future basis for efficient and pertinent data collection.

We had hoped to explore simultaneously protocols concerned with three types of opiate addict: a) those who had been recently detoxified coming directly off the street; b) those who were at high risk of relapse even though currently drug-free, such as patients returning to the street after a term in prison, in which a condition of parole would be the entry into some treatment program, and c) those who were detoxified after a long course of methadone maintenance treatment. These goals were worthy, but as things turned out, they were not very feasible for a number of reasons.

We anticipated that many patients would be potential candidates for treatment and that it would be important not only to know what sort of patients entered treatment but also what sort did not. A high refusal rate was expected, but even with the most liberal projections, we never fully anticipated the small yield of patients eventually attained. We also expected that of those actually entering treatment, a high dropout rate would be encountered. Here, too, our advance estimates, even though realistically high, were far short of the actual experience,
There was some concern that patients assigned to placebo might overdose by experimenting to see whether or not they were on the antagonist or on the placebo. This concern was not substantial, for we felt that no one would be likely to use an initially large dose Until a smaller one had first failed, in which case they might try to overshoot the antagonist. Both at the time the study began, and for most of its duration, heroin of considerable potency was simply not available on the street. We, expected an amount of experimentation which might make the "blind" aspect of the study only relative.

So we embarked on a phase III study on a drug still Undergoing phase II trials. When politicians want answers, they want them fast. Or if they don't get answers, at least they want fast action. The conditions Under which this study was inaugurated were certainly far removed from those which would ordinarily be done by deliberate, thoughtful clinical scientists.

Well, where do we stand almost three years later? Was the entire CENA study a monumental waste of time, effort and money, one of those vast cost over-runs which hasty expediency in governmental affairs breeds? The answers are partly "yes" and partly "no".

The CENA study demonstrated the feasibility of doing a controlled study of narcotic antagonists. Naltrexone was successfully compared against a placebo, and were one given enough sample size possibly significant differences might be shown. Still, this comparison is made at an enormous cost, and with such a high rate of attrition as to leave the results obtained, whatever they may be, somewhat questionable. The extraordinarily small sample of all potential candidates for the study represented by those groups which completed treatment for any appreciable period of time creates an enormous negative bias. One must assume that only the most highly motivated patients were ones who entered and stayed, and these would be quite naturally those who least needed any specific assistance. Thus, should we show a statistically significant difference between those treated with naltrexone and those treated with placebo in regard to staying in the study or in their use of opiates while in the study it would have been accomplished against this negative bias. Should we fail to show any such differences, we shall not be sure that we have truly failed to find a difference between the two treatments. Even

under the best of circumstances, a no-difference result proves little, but in this situation it would prove nothing.

The CENA study has culled out a lot of information that for one reason or another seemed to be worth gathering, so that it might now be possible to arrange for a data collection system for future studies which would be far more efficient and pertinent. Unfortunately, we did not take the time to test the reliability of the data we collected. When dealing with such unreliable sources as addicts themselves, such reliability studies are a major concern.

The CENA study has probably been most valuable in proving that naltrexone can be given in the rather liberal dosage schedules postulated with a great deal of safety. Without the inclusion of the placebo control, several issues concerning its safety would have been raised. The placebo control provided reassurance that the drug was acceptably safe, regardless of how efficacious it may ultimately be found to be. Other uncontrolled clinical trials run concurrently with the CENA study confirm the safety of the drug.

So where are we now? Data collection has been concluded and the data analysis and summary report should be completed before the end of the year. It is most unlikely that the CENA study will prove the efficacy of naltrexone as a treatment for opiate addiction. Rather, it will point out in a most forceable way that oral naltrexone will be an acceptable, and probably highly effective, treatment only for patients whose desire to rid themselves of the opiate habit is so great that the contribution of the drug as compared with placebo is extremely hard to assess. One will be able to say that this sort of treatment can be offered patients with some assurance that they will not deliberately overdose in an attempt to overshoot the blockade of the drug and with some assurance that for moderately long-term treatment the drug is safe. Future studies evaluating treatment of opiate addiction will have available a standard set of pertinent data to assess the results of treatment.

And so naltrexone remains a paradox. Clearly, this treatment could make the use of opiates totally unrewarding. It seems unlikely, if not impossible, that many addicts could obtain enough heroin to overshoot the blockade produced bv these doses of naltrexone. Thus, from a pharmacologic viewpoint, the drug is an assured success. The paradox is-that it can't be delivered. When offered as an intermittent oral dosage schedule to suitable candidates for treatment, it is acceptable only to a small minority, only a few of whom persist in taking the drug for any period of time. The paradox is that we have a good drug which we can't give away.

But this paradox may not be unsolvable. One can hope that other delivery forms of naltrexone may mitigate these problems and that it might still live up to the promise which only a short time ago made its study such a matter of high priority.

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VARYING CLINICAL CONTEXTS FOR ADMINISTERING NALTREXONE

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The employment of narcotic antagonists in the treatment of opiate dependent individuals is a subject of growing importance and attention. The by-now traditionally accepted modalities of methadone maintenance and therapeutic communities both have their various disadvantages which do not require reiteration here. It is sufficient to recognize that alternatives to existing treatments for opiate dependence would be highly welcome.

While the existence of narcotic antagonists has been known as long ago as 1915 (Jaffe, 1975), actual work in applying narcotic antagonists to the problems of opiate dependent patients in a systematic clinical way has spanned perhaps a decade at most of recent history. Much of the work that has been done so far has been predicated on the concepts of experimental extinction of both classical and operant conditionings of drug seeking behavior as described by Wikler (1964). Work has been done with Cyclazocine and with Naloxone (Jaffe 1975) which has established these agents as effective but limited modalities. Cyclazocine is recognized as having long duration but unpleasant side effects for some patients, while Naloxone exhibits a short duration with minimal side effects.

When Naltrexone was synthesized (1965) it was soon recognized as partaking of the best qualities of both Cyclazocine and Naloxone and as such, seemed to be an outstanding candidate for the further exploration of the possibilities of narcotic antagonist therapy. Naltrexone was found to have little or no side effects and a duration sufficiently long so that a single oral dose could be given to block euphoriant effects of heroin for 24, 48, or even 72 hours if the dose were sufficiently large (Resnick, 1974).

Naltrexone has thus become the subject of a number of investigators who are studying the safety and efficacy of antagonist therapy. As these questions have been dealt with (namely, safety and efficacy), a third dimension of Naltrexone's usefulness, which might

be called its applicability, has increasingly become the object of attention. Granted that Naltrexone works, for whom will it work best and longest? Put another way, who will be willing to take this substance which is not addicting like Methadone and not confining like a residential program? Naltrexone is a cure in search of an audience. Thus, three questions have to be asked about this substance- is it safe, is it efficacious, and is it applicable?

At this time the first two questions have been sufficiently answered by other researchers (Resnick et al. 1974, Martin et al. 1973) as well as the research conducted at this clinic (which is described below). The third question remains unanswered and is the primary focus of this paper. In a detailed fashion, varying clinical contexts for administering Naltrexone are described and used as a medium through which the investigators believe some clarification concerning this question can be sought. In the following sections, the programs are first described and then the results of these programs will be given under three headings: Medical Observations, Program Retention and Attrition, and Other Relevant Findings (about factors associated with programmatic success). After this, some brief conclusions are offered and a glossary of the abbreviations used in this paper is given.

Naltrexone has been under clinical investigation in the Drug Dependence Unit of the Connecticut Mental Health Center since 1973. The process has not been a continuous one, and the breaks in time have served to divide the work into three phases which we will call Naltrexone I, Naltrexone II, and Naltrexone III (in the figures these phases have also been called Naltrexone First Series, Naltrexone Second Series, and Naltrexone Third Series).

Before the programs under these titles are discussed a summary is given of the Low Intervention Program and the patients treated in the clinic.

PROGRAM FORMAT

The Low Intervention Program is a component of the Drug Dependence Unit of the Connecticut Mental Health Center. In this facility, narcotic addicts are treated with twice a week group therapy (two 90-minute sessions, in the evenings, of a modified encounter type) and individual counselling on an as-needed basis. The patients are also required to void three urines per week on a random basis, and ingest narcotic antagonist medication according to schedules dictated by the research protocols employed. At that point in the program in which an individual's narcotic antagonist therapy is terminated he continues to be treated with the basic modalities of the program, i.e. group therapy and urine testing, until such time as he is deemed ready for discharge by the staff. This judgment is made only after deliberation by the staff and involves an assessment of the individual's programmatic adjustment as well as his overall life adjustment. The general time model employed in making these judgments has been about one year for those individuals who stayed with the program. Concretely, in the Low Intervention Program the typical experience for a patient has been to go about his business of being either a worker or student during the day and then to attend group therapy two evenings a week and to void three urines per week according to a randomized schedule. During this time he has had the two official contacts with group therapy, as well as a number of informal contacts with both counsellors and nurses incidental to his voiding urines, taking medications and undergoing medical testing, In addition, as mentioned earlier, the patient has also been subject to individual counselling when this was felt to be needed. It will be noted that there has been a stress on the function of the patient above and beyond his managing to come to the program. This will be further elaborated on in the discussion of the patients. The staff has consisted of a director, three ex-addict counsellors, two nurses, a research associate, a secretary (all of the above on a full time basis) and a part time internist as well as consultants on a limited basis. The same approximate staffing pattern has been maintained throughout, although there have been some variations largely with respect to the number of clinical personnel whose number was in turn determined by the census of the clinic.

Patient Population

The patient population studied in the three phases of Naltrexone research, has been defined, first of all, by the criteria of inclusion/exclusion which have been used throughout. Where there have been changes in the criteria which in fact have always been minor, these changes will be noted in passing. The criteria of inclusion have been maleness, age of 18 to 45, and a verifiable history of opiate dependence (at first a rigid criterion of two years of opiate dependence was called for; by the time of the Third Naltrexone Study, which was done under the aegis of NAS, this requirement had been changed to any period of verified opiate dependence with a lower limit set at about six months - in fact, most patients admitted to the program had longer drug histories than this lower limit and the average was

greater than two years). Patients to be excluded were essentially those suffering from mental and/or physical illness sufficient to either (a) cause absence from the program or (b) necessitate continuing medication (which might cause unknown reactions with the experimental drug employed in the study and/or confound the evaluation of physiological and subjective side effects). Besides the change in stipulated length of prior opiate usage, there was also a change made in pre-program drug status requirement. At the beginning of the NAS (Naltrexone III) Study, it was stipulated that only currently non-addicted patients would be accepted (currently addicted patients were being studied in other NAS-sponsored research). This was felt practicable at the time in anticipation of intake of freshly discharged prison inmates. What eventuated was that the predominant referral to the program was not a fresh prison discharge, but a person who had already been on the street for some time, often using drugs right up to a level of being readdicted. After several months then, the admission criterion was changed back to one which was used in earlier studies, i.e. men verified through history, physical and urine tests as currently addicted were given a preliminary Methadone detoxification. The other descriptions of our population derive not from program criteria but from demographic factors which describe our patients, in the average case, as young (mean age 24.69 years) adult males, almost equally black (54%) and white (46%) who come from urban addresses, and are of generally low or moderate educational (mean 11.3 years of school) and socio-economic status and who typically have been in one or more programs before their referral to us. In addition, a standard of the Low Interventfon Program (which was designed to make rational the application of the low intervention structure to an addict population), i.e. the holding of a job or a place in a full time educational or skill program and/or demonstration of social stability by maintaining a household or relationship - was imposed but not with the utmost of consistency. For one thing, the uncertain employment situation of the last few years precluded the rigid enforcement of the employment requirement: for another, the judgment of social adequacy, while clear, in some cases, could not be made with certainty in others. In the long run, the LIP criteria of vocational and social stability were used as guidelines but not as definitive or rigid standards.

Overall then, our population has been a fairly homogeneous group consisting largely of males of low educational and socioeconomic status and considerable treatment experience.

Experience with Naltrexone at the Low Intervention Program (Three Series)

The three programs which have employed Naltrexone at the Low Intervention Program will now be described briefly, in chronological order, before the results are presented in a later section.

The first series was initiated in June 1973 and had an intake phase which ran until September of that year. The program was started on an inpatient basis in order to provide close monitoring of physical and psychological functions in this early phase of Naltrexone research. The research protocol called for inpatient treatment of the first ten patients. Twelve patients were actually accepted into this phase; of these twelve, ten completed the inpatient phase. One of the patients showed signs of acute hepatitis and was withdrawn from the study; another patient was quite uncooperative shortly after being brought into the hospital and kept referring to his need to take time off in order to attend to personal business. This patient was induced twice and still drifted away after these two experiences and was then discontinued. He was heard from at a later time when he applied for Methadone maintenance in another state, and he was then again heard from at still a later time when he was eventually treated with Methadone again, in this area.

The ten inpatients were kept for an approximate inpatient stay of 28 days (some were actually discharged a bit sooner than this). This 28 day period was in keeping with the floor policy at the Connecticut Mental Health Center where the work was started. Following their inpatient stay, the patients were converted over to outpatient treatment at the Low Intervention Program. After these patients had been transferred over, another five patients were enrolled, and these individuals started as outpatients from the very start. Thus, there was a total of 17 patients who were ever on Naltrexone in this first series and of these, 15 were on it for at least a substantial period of time. These patients were all inducted onto the drug by ten mgm. daily increments up to a level of 50 mgms/day and they were then treated for 7 days a week with 50 mgms on each day. This treatment was continued for 90 days and then, in accordance with the protocol, medication was stopped. The individuals were then kept on the program, as has already been described before, for an average duration of about one year. It might be noted in passing that not only did about 2/3 of the patients begin in an inpatient atmosphere, but they also began in a general ambience of optimism and enthusiasm which was shared by patients and staff alike. The advent of Naltrexone as a modality had been preceded by very favorable publicity, and

this publicity was perhaps all the more favorable by virtue of being gained at the expense of the outgoing Cyclazocine project which had acquired a reputation for offering an unappealing and unpalatable substance. A number of patients were heard to remark that they felt surprisingly good and cheerful and were happy tp discover that there were very few side effects associated with the drug. All patients were given physical and neurological examinations. CBC, LJA and SMA-12 were done weekly for the first month and then on a monthly basis.

Second Naltrexone Series

As already stated the intake on the first series of Naltrexone patients was begun in June 1973 and continued until September 1973. At that point, further intake into the study was halted by a directive of the Food and Drug Administration and thus no new referrals could be taken. At this point, new referrals were largely diverted away from the Low Intervention Program to other components of the Drug Dependence Unit. Nonetheless, some patients were still referred to Low Intervention because it was felt by personnel at the screening unit that these individuals were particularly suited to a low intervention system. These individuals who were eventually to number 15 in all, were taken into the Low Intervention Program and' treated essentially with the same programmatic structure as had been applied to their predecessors. These patients were now treated with the antagonist drug Naloxone, with a dosage of 800 mgm/day. This dosage was, of course, not a 24-hour blocking dosage. The medication was given in the late afternoon in an attempt to deal, hopefully, with the higher risk thought to be associated with the evening period of each day (Kurland et al. 1973). During this period of accumulation of 15 patients, the individuals were treated as the patients had been in the earlier series except for Naltrexone and then, when the ban on Naltrexone induction was lifted by the FDA, these individuals were converted over to Naltrexone with the same kind of induction and the same kind of maintenance schedule as had already been employed. The program duration was now set at a 6 month period in accordance with the FDA regulations of that time. In all other respects, the treatment program and philosophy was identical with that accorded the first group. As will be seen later in the discussion of results, this series happens to have included a larger than average proportion of atypical outcomes. The reason might be that the favorable publicity attached to the first series had caused a reaction among the screening personnel such that they responded to requests on the part of some individuals to be sent to a low intervention program where the excellent new drug could be obtained. This may have attracted some individuals who were perhaps at this point responding to something of a fantasied quality believed to be associated with Naltrexone. Medical testing indentical to the first series was carried out on this group except for the dropping of the EEG.

Third Naltrexone Series

The intake for this second series occupied the first few months of 1974. During this time period a series of discussions was held with the NAS-NRC (National Academy of Sciences- National Research Council) with a view toward undertaking a new protocol for studying Naltrexone. The Committee on Clinical Evaluation of Narcotic Antagonists at NAS had conceived a double-blind drug vs. placebo design which would test out as searchingly as possible the true impact of Naltrexone in the areas of both subjective and objective effects. This protocol also would have the effect of maximizing the potential for individuals' motivation in wanting to test out the effect of their medication insofar as the very nature of the program could very well arouse curiosity in the patient's mind as to whether he was indeed blocked against the effect of narcotic drugs. The provisions of the NAS study included a very thorough medical evaluation of each individual. Among other tests, the protocol called for a slit lamp examination of each patientls eyes (the earlier series had called for EEG examination of the patients, but this requirement had been dropped by the time of the NAS study). Physical examinations and neurological examinations were done at baseline (and also repeated every 3 months). Chest films were done at baseline and termination. CBC, UA and SMA-12 were done monthly. Australia antigen, VDRL and special hematology were done at baseline and termination from program.

Since, by this time, the feasibility of giving Naltrexone on a three-day a week basis had already been well established, the NAS protocol called for dosages of 100 mgm on Monday and Wednesday and 150 mgm on Friday. This schedule followed an induction done by 10 mgm increments up to the 50 mgm level. The 100 mgm and 150 mgm dosages for 2 and 3 day periods had been proven effective by Resnick (Resnick, 1974).

The NAS Naltrexone study then began in August of 1974 and continued intake until

July 31st, 1975. In this 11 month period a total of 73 patients were logged, but just 54 patients actually ingested drug one or more times. In the early phase of the study, a number of patients were logged in and assigned bottles of study medication who actually did not show up after a single initial contact. This included ineligible and uninterested patients. It was then decided not to assign an NAS number until the patient had completed certain preliminaries and was almost ready for medication. This sharply reduced the number of "No Starts". The findings of this study, which has been called Naltrexone III, will be given along with the other results in the following section.

Results I - Medical Observations

One fundamental aspect of exploring the usefulness of Naltrexone is the area of medical safety. This new substance had been used with laboratory animals and a limited number of human volunteers (Martin, Jasinsky & Mansky 1973) but was still in an early phase of scientific knowledge when first used in our programs. Accordingly a comprehensive set of medical and neurological evaluations was carried out in each of the three Naltrexone phases. As a matter of fact, the examinations required were identical in Naltrexone First Series and Naltrexone Second Series, and almost the same in the Third Series.

The tests called for in the First and Second Series were the following, done at baseline: (1) chest film, (2) Tuberculin test, (3) EKG, (4) EEG, (5) urinalysis (with microscopic, (6) CBC with differential, (7) FBS, (8) BUN, (9) Uric acid, (1) Liver function tests - total protein, albumin, bilirubin, alkaline phosphatase, SGOT and LDH and, (11) Serum testosterone.

Following this, certain tests were done weekly: 1) CBC 2) urinalysis 3) BUN 4) Blood uric acid 5) liver function tests (as above).

Finally, certain tests were done monthly and at termination: 1) EKG, serum electrolytes, testosterone and EEG.

In the Naltrexone II Series, all tests were done exactly the same except for omission of the EEG and serum testosterone tests.

In Naltrexone Third Series, the following tests were done at baseline, monthly and at termination: (1) CBC with differential, (2) SMA 12-60 including FBS, BUN, uric acid, inorganic phosphorous, calcium, cholesterol and liver function tests including total protein, albumin, bilirubin, alkaline phosphatase, SGOT and LDH, and urinalysis. The following tests were done at baseline, third month and termination: (1) Reticulocyte count (2) platelet count (3) prothrombin time (4) chest x-ray (5) slit lamp examination and (6) EKG.

Certain physical measurements were done regularly: (1) blood pressure was taken weekly and weight was taken also on a weekly basis.

Physical examinations, psychiatric interview and neurological examination were done at baseline, third month and termination.

The results can be dealt with in various ways but are perhaps most easily dealt with by categories, first for Naltrexone First and Second Series and then for Naltrexone Third Series.

With respect to the first and second Naltrexone Series, the following can be said: 1) No changes were seen in chest film. There were a few instances of mild fibrotic changes and increased hilar markings, 2) The only positive Tuberculin tests seen were worked up further with no evidence of active disease. 3) There were no EKG changes attributable to Naltrexone! one individual was seen with PVC's and treated with quinidine with good result: he had been mildly symptomatic for years and felt better when treated. 4) There were no EEG changes before, during, or after Naltrexone. The only changes seen, of a very minor degree, were in a beneficial direction. 5) Urinalysis in this group (as with the later group) not uncommonly showed WBC's and other evidence of urinary tract infections - these were followed, cultured and treated by the internist. There was one instance of possible albuminuria which did not prove out on 24 hour studies to be significant. 6) The only CBC changes noted were attributable to familiar sources of pathology - e.g. viral infections. There were no prolonged or inexplicable changes of red or white cells. 7) FBS was normal throughout; some seeming irregularities found were due to non-fasting condition of patients who, on retest, turned out normal. 8) BUN was almost uniformly normal: where abnormal it was only slightly elevated and did not change in the study. 9) Uric acid elevations were seen in several individuals - these were of mild degree and did not change with Naltrexone administration. 10) Liver function tests showed by far the greatest percentage of abnormality - for example, only 4 of the 17 patients in Naltrexone First Series showed consistently normal SGOT levels and of these 4, two were teetotalers. Almost all patients

in this and later series used alcohol, many quite heavily, also, many had positive histories for hepatitis. It was noted that several patients had gradual reductions of SGOT levels (and also, of LDH, bilirubin and alkaline phosphatase levels) when they were hospitalized (which gave them an alcohol-free rest). Similar reductions were seen during outpatient alcohol abstinence reported by the patients. Episodes of acute hepatitis were not uncommon: one in Naltrexone I Series exempted the patient from this series and this was repeated in Naltrexone Series II. Serum testosterone levels varied considerably but all within a normal range and this test was later dropped from the battery.

In the Naltrexone Third Series, the results were comparable to those seen earlier. Thus, changes in the white blood count and differential, while common, were always transient and associated with identifiable pathology. The SMA-12 battery results were generally unremarkable except for (again) a very high percentage of abnormal liver function tests - most commonly, elevated SGOT's and altered plasma proteins, usually elevation of gamma globulins and serum immunoproteins. (IgM, IgA, and IgG).

These elevations were again related to our patients' histories of alcohol use and/or bouts of hepatitis. Very often, a curve could be traced in the more sensitive liver function tests, such as SGOT, in which the blood chemistries would reflect quite accurately the rising and falling rate of alcohol intake as described by the patient. As in the earlier series, there were several instances of acute hepatic pathology accompanied by clinical manifestations of liver disease - in such episodes, the program internist made a clinical judgment about the patient as to whether to continue or discontinue his medication. In several instances, medication was stopped because it was felt that it would be improper to continue experimental medication in the face of acute illness. One such individual left our study under the heading of "Non-responsible drop-out"; another, who had completed 150 days on the program, was called a successful terminator. Medication was always stopped if the liver function tests became worse without alcohol ingestion. In all, 5094 laboratory examinations were performed on the Naltrexone Series III patients. Of these, 436 or 8.5% were abnormal. Of this number, 277 or 63% related to liver function and another 99 or 23% related to urinalysis findings (typically, WBC in urine). This left 60 (13%) abnormal findings scattered over a total of 54 patients: none of these was associated with demonstrable pathology.

One test that caused a moment of concern was the slit lamp examination. By May of 1976 only two completers of medication had had this final slit lamp examination. At this time, both showed retinal pathology (retinal holes in one case, a horse-shoe shaped retinal tear in the other) that had not been seen at baseline. Although a remote possibility, it seemed necessary to at least entertain the idea of Naltrexone's association with retinal pathology. The double-blind code was broken for these two individuals. The patient with the most pronounced pathology was on placebo drug; the other patient was on an active drug. When the next 20 patients had their final eye examinations without significant observable change it was then possible to make an estimate of the incidence of retinal pathology in this sample and compare it with a general population - they were found to be comparable and this placed our findings in the region of normal expectancy. Consultation with our own ophthalmological consultant as well as the scientists monitoring toxicology studies, and an extensive literature review all confirmed the proposition that there is no evidence of direct effects of opiate antagonist on the retinas of the various species studied, including man.

No other areas of medical testing yielded any significant abnormalities. Throughout, the physical and neurological examinations were remarkably constant, with the changes noted above. Changes of psychiatric status were, in this population of young adult male addicts of varied backgrounds (including, frequently broken homes, years of crime and incarceration, and of course, the usual crises of early adult life) not uncommon but there were no changes seen that were not anticipated in their pre-Naltrexone histories.

Symptom Side Effects

The area of symptom side effects deserves a more detailed discussion but can be covered superficially at this time simply by stating that, in general, Naltrexone was well tolerated and accepted. Most subjective complaints were mild and even absent in some individuals. The one recurring complaint heard with some regularity was that of abdominal discomfort. This was usually a sense of either constriction or heaviness in the epigastric and/or lower abdominal area. It rarely went as far as producing either cramps or pain. There were three individuals, however, who were discontinued on drug due to abdominal complaints. The first patient, L.W. (NAS 016) was found to be suffering from a viral syndrome and moderate hypertension soon after starting the program, and he began to complain of nausea and vomiting while suffering from the virus. After the virus cleared up, he still had repeated nausea and vomiting. He was started and stopped twice on

Naltrexone; each time, resumption of medication caused recurrence of nausea end vomiting. He was then stopped on medication with cessation of symptoms and carried on the program, He was receiving treatment for his hypertension throughout with very gradual response. L.W, dropped out about a month after this - he was heard to have returned to drugs but a more recent follow up showed him to be drug free,

Another patient, F.T. (NAS 028) complained of chronic abdominal discomfort, sometimes progressing to nausea and vomiting: at other times, crampy (but not diarrheic) bowel movements. He also complained of green bowel movements (which indeed were green by inspection - laboratory analysis failed to disclose any unusual findings) . He was taken off medication, felt better, returned to medication with recurrence of symptoms and then stopped (whereupon he again felt well). Evaluation of his case has always remained slightly unsettled because F.T. is an admitted heavy consumer of alcohol who also felt better when he reduced his drinking. His medication had to be discontinued, however, when it seemed that the combination of alcohol and Naltrexone was, for F.T., an unworkable combination.

Two other individuals, K.A. (030) and W.H. (067) complained of moderate but persistent abdominal discomfort and spontaneously asked to be put back on 6 day-per-week Naltrexone, rather than 3 day-per-week Naltrexone regime. It should be understood that the total weekly dosage is the same in these two systems but that the 6 day system involves smaller doses and was felt by these two individuals to be more tolerable. This would appear to verify that Naltrexone is, at least for some patients, a gastrointestinal irritant but it can also be noted in passing that the two individuals in question are somewhat more dependent than some of their colleagues and may conceivably have also been desiring more frequent clinical contact. This latter possibility is really mentioned for the sake of completeness; it is believed that the two patients were registering genuine abdominal discomfort (since it was also mentioned by others) and that these two responses may indicate some limitation in Naltrexone dosage for at least some individuals.

Both patients said they had always had "nervous stomachs" which had been treated conservatively by their doctors. Still another patient also requested the 6 day system, in fact, he asked for a 7 day medication regime. This man, R.G. (NAS 071) had by age 23, an 8 year history of "nervous stomach". When his gastric symptoms grew so severe as to require suspension of medication and a GI series (one of many in his life), the double-blind code was broken for another reason, and he was found to be on placebo. This case certainly underscores the highly suggestible character not only of this particular patient but probably of many patients with functional disorders of the intestinal tract, including the case mentioned earlier.

There were no other frequently or systematically mentioned symptom side effects noted in our population.

Results II - Program Retention and Attrition

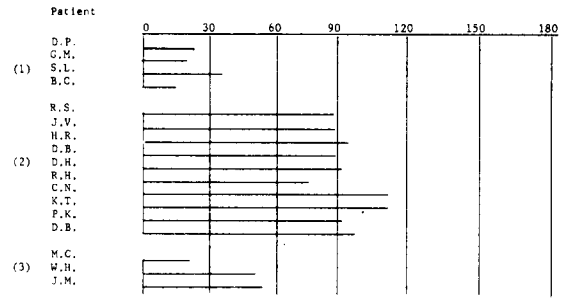
The results for the first Naltrexone series are shown graphically in Figure 1. In this figure, as in later figures, it will be seen that three categories of program outcome are given for our patients. First category is "Split" or "Responsible Drop-out", in which the individual leaves the program prematurely and of his own volition or apparently of his own volition. The next category is "Graduation or Termination in Good Standing", and this title should be self explanatory. It indicates a successful outcome. The last category applied is "Obligatory or Non-responsible Drop-out" and this indicates individuals who are removed from the study due to some extraneous and apparently uncontrollable reasons such as having a medical problem, or relocating outside our clinic area, etc. In Figure 1 it can be seen that the first 4 patients in this series are classified as "Self-responsible Drop-outs or Splits" and this is 20% of the base number (the base number is the total minus the non-responsible drop-outs). The next 10 patients successfully completed the drug phase of the program (this is in distinction to the post-drug clinical phase of the program), and this represents 71% of the base number 14. The last three patients are called "Non-responsible Drop-outs" and are 3 of 17, or 17% of the total N. It can be seen that the number of non-responsible drop-outs has been subtracted in this and subsequent totals in order to make a more rational base - by definition, the non-responsible drop-outs are those who leave drug and/or program for reasons not obviously attributable to their own volition, e.g.: intercurrent illness, etc. Patients in Naltrexone I who went on to successfully graduate from the program (which involved a considerably longer period of time than the 90 days devoted to Naltrexone) were relatively few in number (three in all). Here, as in subsequent series, it has developed that there can be a large disparity between completed time on drug and completed time on program. (It can also be seen here, however, that the disparity was maximized in the First Series and this is probably due to the simple fact that in the first study, medication could only be

given for three months while the program duration was for 12 months, and during this time a number of individuals began to relapse into their pre-program habits). At this point it was believed that the relative brevity of antagonist administration was responsible for this disappointing decline after an excellent beginning.

In summary it can be said that retention was high for a short period for a group which had predominantly an inpatient beginning and a daily medication schedule. This was also a group existing in an atmosphere of optimism and enthusiasm about a new modality which had received favorable advance publicity.

In Figure 2 the results of the Second Series, called "Naltrexone II", can be seen. It will be recalled that this group of patients followed the initial series when intake was resumed for the Naltrexone project. The results of this series, which is shown in Figure 2, does, to a certain extent, defy conventional analysis, As has already been mentioned earlier, the number of atypical outcomes provided a temptation to construct a larger number of categories than the three we have been using in this presentation. It was decided to resist this temptation, however, and explain the unusual outcomes as follows: (1) Patient Number 1, M.S., left the program after his court case had been adjudicated. At this point he revealed that he had really been masquerading as an addict to camouflage his real identity as a dealer in drugs (primarily) and only a moderately heavy, but not addicted, user of heroin (secondarily), (2) Patient number 6, J.M., deliberately challenged Naltrexone in such a frontal and reckless way that it was debated at great length as to whether it was wise to restart him on the drug. He was, however, after due deliberation, returned to Naltrexone usage, but he then became increasingly erratic in his attendance in the clinic and his ingestion of narcotic antagonist, He eventually had to be discontinued from LIP and was transferred to a Methadone program. (3) Patient 12, S.B., took a near-fatal overdose of barbituates after an argument with his girlfriend. He was then transferred to a state hospital and from the state hospital to a residential program. (4) and (5) involve patients 13 and 14. Both of these patients showed increasing disorganization after being on Naltrexone. This developed rapidly with Patient 14, who became catatonic and paranoid and had to be treated with phenothiazines, and eventually, in addition to his individual therapy, required transfer to a Methadone maintenance program. With individual 13, loss of organization took place in a more gradual way, but was marked by clinical signs of increasing depression

FIGURE 1

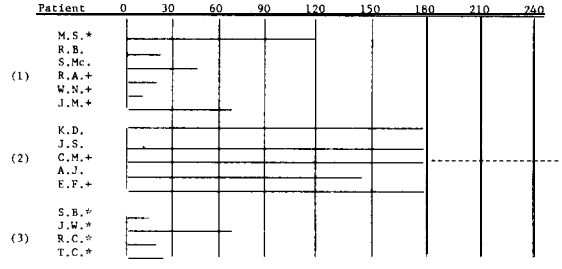


NALTREXONE FIRST SERIES
DAYS ON DRUG

(splits = 1, completers = 2, and obligatory drop-outs = 3)

and dependence which caused him to spend long hours at the clinic in which he would seek out the companionship of the clinic staff. He began to periodically use amphetamines, which he described as the "only antidepressant that allows me to socialize." This resort to amphetamines took place after he had declared a trial of both Elavil and Triavil to be ineffectual. It is true that both of these patients, number 13 and number 14, did have a previous psychiatric history, but at the time of admission, they seemed fairly well integrated, and it did not seem that they would be unworkable in the study. It may have been the loss of the tranquilizing properties of their narcotics that caused these two individuals to lose their state of adjustment. There was no reason to suspect that Naltrexone was productive of their psychic distress, especially in view of their

FIGURE 2



NALTREXONE SECOND SERIES
DAYS ON DRUG

(splits = 1, completers = 2, and obligatory drop-outs = 3)

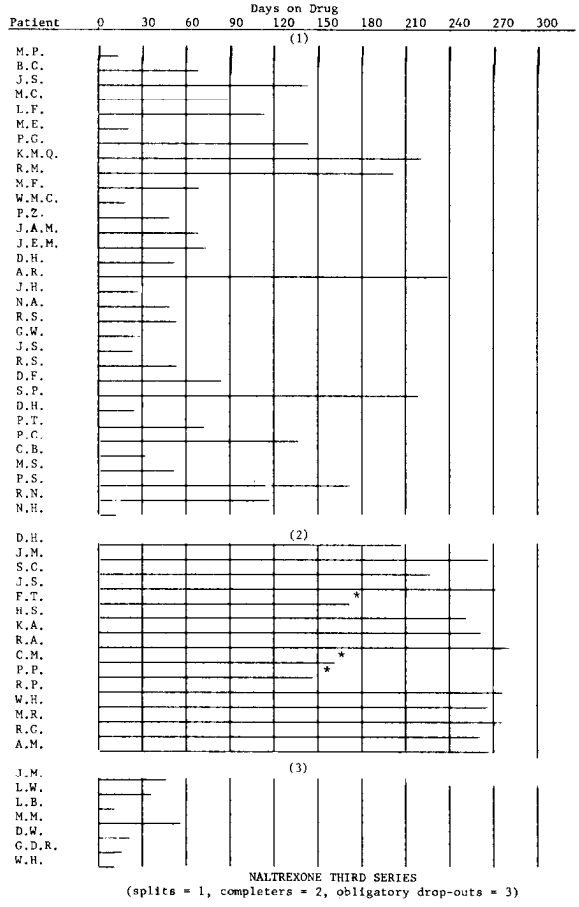
*Atypical outcome - see text
+Started directly on Naltrexone without prior Naloxone

prior histories. (6) Patient number 15 relocated to a distant part of the state which was beyond commuting range. Overall, we have ended up classifying 4 of these 6 atypical cases as "Non-responsible Drop-outs" for the reasons given. This relatively high loading of 4 cases out of 15, or 26% of the total group, is somewhat high for this category (in the other 2 series, corresponding proportions of the non-responsible drop-outs were 17% and 13%) and this high percentage had the effect, of course, of reducing the percentages scored by the other 2 groups. In any case, the percentage of successful medication completions was considerably less than in the first series, at 45%, and the percentage of splits, or self-responsible drop-outs, rose to 54%, which is slightly more than half the sample.

In summary, then, 15 patients, of whom 10 had been on Naloxone at the start, were treated with Naltrexone for 6 months on an out-patient basis. The series was marked by a number of atypical developments. The results of 54% drop-out, 45% completion of medication, and 26% non-responsible drop-outs seem not as representative of our population in this series as they have been in others even though they were ostensibly drawn from the same pool of patients. The reader should note that two patients admitted to challenge.

The results of the Third Naltrexone Series are shown in Figure 3. It should be pointed out now before the table itself is inspected that about 1/3 of this group of individuals did end up testing or challenging the drug or the program in which the drug was offered. (The program was a double-blind, active drug vs. placebo study). This phenomenon will be discussed again later on, but is mentioned at this point because of its importance. In Figure 3 it can be seen that the total N in this series was 54, and that 7 of the 54, or 13%, were characterized as being non-responsible drop-outs. The remaining base number of 47 (54-7) thus yields percentages of 68% split and 32% satisfactory completion, including three patients who were allowed to stop medication early due to extraneous reasons judged acceptable by the staff. These patients are marked by an asterisk in Figure 3. One patient was taken off drug at the internist's advice, due to abdominal problems, one patient left the program, with approval, for a full time day job and full time night school and one patient was encouraged to leave by his parole officer. All of these patients had been proceeding normally, with good performance at time of medication stoppage. All three kept regular contact with the program.

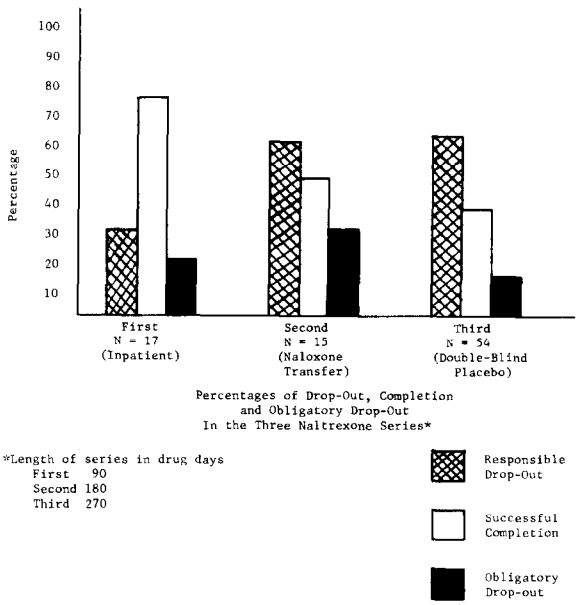
FIGURE 3



*Premature completers (described in text)

It would be tempting to speculate that the lower percentage of satisfactory completions was due to a linear negative relationship between length of program and rate of retention, which is graphically depicted in Figure 4, where there is an almost straight line decline from the first through the third program as these programs become longer in their drug ingestion period. It should be borne in mind, however, that the qualitatively different nature of the third series, which was a double-blind study, makes it difficult, if not impossible, to make this kind of quantitative comparison. It can be seen, for instance, that when the same material is also looked at, first in Tables 1, 2, and 3 with raw numbers, and then in Figures 5,6, and 7 with percentages, that it become: even more unclear as to whether there really is a linear

FIGURE 4



relationship between time on program and number of attritions even though this can be roughly identified in the figures. In the same figures it can also be seen that there is in the first 2 studies, which employed an open approach to the drug, an eventual decline to a zero degree of attrition so that it might then be argued that the unusual table in this series is the third table which is a double-blind experiment. In other words, it is conceivable that if the third series had involved an open plan for administering Naltrexone, a zero rate of program attrition might also have achieved, but could not be achieved because the knowledge of the patients about the placebo vs. active drug plan provided a constant provocation for further challenge which led to eventual readdiction and discharge. It might also be noted at this point that the peak seen in Figure 7 at the 150 day mark which is underlain by a dotted line representing another hypothetical outcome, is probably an artifact due simply to the fact that three individuals violated program rules around the 150th day in the program, This particular rule was concerned with the carrying of weapons in the program, and the 2 individuals who refused to obey the regulation of the program were discharged and the third individual who had complicity in the affair was also discharged at the same time. This was an unusual and atypical event which produced the attrition peak at the 150 day mark and probably would not recur soon again in a similar series.

To continue this discussion of attritions one more step, it can also be argued that the decline between the first and second series while again possibly related to the temporal increase of 90 days to 180 days of drug nonethe less also seems to have involved a qualitative shift from an "average" group of patients to an unusual group of patients as has already been described above. If this was the case then there might not have been as evident a decline and the seeming slope which can be imagined in Figure 4 may really be an artifact.

The phenomenon designated as challenge has already been mentioned - it is illustrated in Figure 8 and in Tables 4, 5, and 6. First, it should be explained that "challenge" originally designated any opiate usage by any patient during a time that he either <u>was</u> on Naltrexone or was <u>supposed</u> to be on Naltrexone - obviously, different <u>kinds</u> of situations. The overall results are in Table 4. At first, it was

TABLE 1

Frequency Distribution of Responsible Drop-outs in First Naltrexone Series, N = 14

Number of Days	0-30	31-60	61-90
Frequency	3	1	-

TABLE 2

Frequency Distribution of Responsible Drop-outs in Second Naltrexone Series, N = 11

Number of Days	0-30	31-60	61-90	91-120	121-150	151-180
Frequency	3	1	1	-	1	-

TABLE 3

Frequency Distribution of Responsible Drop-outs in Third (Double Blind) Naltrexone Series, N = 47

Number of Days	0-30	31-60	61-90	91-120	121-150	151-180	181-210	211-240	241-270
Frequency	10	8	3	1	5	1	1	:	2

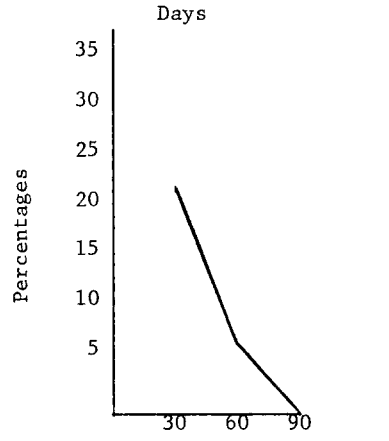
thought that there would be few instances of unwarranted absence from antagonist. This turned out not to be the case. In Tables 4, 5 and 6 there is a column called "miss med" which shows the number of missed medications. Only one patient in 19 did not miss medication at least once, and the overall average was 10 missed medications, providing more than enough opportunity to use opiates while still in the program. Accordingly, data was then collected under two headings--"direct challenge" referred to opiate usage within 24 hours of Naltrexone ingestion (or 48 or 72 hours after correspondingly larger doses) and "indirect challenge" referred to opiate usage in a Naltrexone free state. Results are shown in Tables 5 and 6. So-called "indirect challenge" could perhaps be better called Naltrexone avoidance, or propam challenqe, or even a refusal to challenge.

Challenges were spotted through urine testing (opiate, quinine and missed urines), combined with clinical anecdotes reported to the staff or elicited by the staff. This questioning was done with circumspection to avoid false positives due to boasting. Each anecdote was judged by an experienced staff including ex-addict counsellors. Since only 6 of 19 patients showed morphine urines, considerable judgment was needed to accept the circumstantial evidence in the other cases. Probably, any errors have been made on the conservative side in estimating the problem. Many patients told of challenging only near termination when it was "safe" to reveal their story. Typically, the patient would say that he "had to know" whether he was on active drug. Interestingly, some patients who said they were sure that they were on placebo did go on to eventual re-addiction (NAS 009, NAS 019) while others said that they knew their drug was placebo but they would not persist in taking advantage of it (NAS 023, 072).

In Figure 8 it is seen that outcome percentages of Naltrexone III challengers as a whole and total group were about the same. This seems to say that challenge of itself does not lead to unsuccessful outcome. This leaves unexplained the fact that retention hit a new low in this series which had a 32% overall challenge rate (40% if one excludes the non-responsible drop-outs). The rates are 22% and 25% for the direct challengers.

In Table 5, the direct challengers show up as a rather stable and long-lived group, with average time on drug of 176 and average program duration of 201. By contrast, the "indirect" challengers in Table 6, who are really Naltrexone nonchallengers, showed average drug duration of 66 days and program duration of 71 days. It seems that the patients in Table 6 first avoided the antagonist and then avoided the program. The large discrepancy between

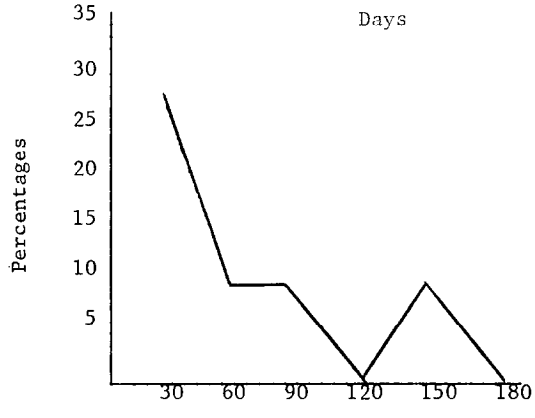
FIGURE 5



Percentage of Responsible Drop-outs by Time in Program

Figure 5: First Naltrexone Series, N=14

FIGURE 6

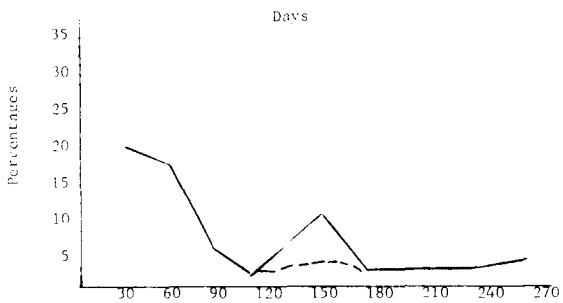


Percentage of Responsible Drop-outs by Time in Program

Figure 6: Second Naltrexone Series, N=1

the "direct" and "indirect" groups seen by inspection is supported by the Mann-Whitney U-test for significance of median differences ($p \leq .01$). Thus, one is left with the impression that patients who challenge antagonist showed a fairly good outcome. At the same time it is true that retention rate hit a new low in this program with its considerable challenge behavior.

FIGURE 7



Percentage of Responsible Drop-outs by Time in Program

Figure 7: Third (Double Blind) Naltrexone Series, N=47

FIGURE 8

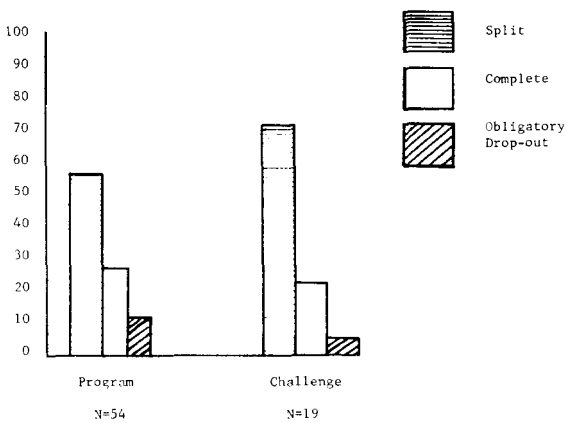


Figure 8: Relative percentages of Outcomes (Splits, Completers and Obligatory Drops-outs) for Third Naltrexone Series as a whole (N=54) and Challengers within the Third Naltrexone Series (N=19)

Results III - Other Relevant Findings

In all clinical research determining what form of treatment is best suited for a particular patient or group is an important question. When these factors or conditions are known a clinician can be discriminating as to whom he treats, thereby making his treatment more effective and efficient. This is particularly important for programs that must depend upon foundations or government grants for their monies, In New Haven, for the past three years an earnest effort has been made to relate the above question to antagonist therapy. As a result of this research we believe we may have: (1) eliminated a sizeable number of factors that are often associated with the question as to what type of addict will benefit most from a narcotic antagonist program, and (2) identified one or two variables that are significantly related to this issue. The manner in which these results were ascertained is important, and hence a detailed discussion of our methodology is now presented. To define our many variables here would be distracting to the reader: therefore a glossary containing our variable set is found in Appendix A.

Our approach to this problem would be best considered intuitive/empirical. No formal standards were applied to the variable selection process. The researchers primarily relied upon data from experimental studies and their own intuitive feeling when selecting a variable for inclusion in the data set. This process yielded a total of thirty-five variables that could be grouped in these divisions: (1) Program Performance, (2) Demographic Data, (3) Drug History.

The distribution within each group in approximately equal; and variables found within each division respectively are: (1) Division One- Elapsed Time on Medication (ETOM), Elapsed Time on Program (ETOP), Required Urines (REQURIN), Number of Missed Urines (NUMISS), Number of Urines Positive for Opiate Drugs (COPIATE), Number of Urines Positive for Barbiturates and Amphetamine Drugs (CBAD), Number of Urines Positive for Other Illicit Drugs (POILLD), Completion of Drug (COMPD), Membership in Naltrexone Series I,II, or III (SAMPLE), Type of Patient Outcome in Study (GROUP), Completion of Program (COMPP), Follow-up Status (FOLLSTAT), and Challenge (CHALLENG). (2) Division two - Age (AGE), Race (RACE), Number of Prior Drug Treatment Programs (PRDRUGTRT), Number of Months in Prior Drug Treatment Programs (NUMINTRT), Number of Arrests (NUMARRST), Months of Incarceration (MOINCAR), Stable Living Arrangement (STABLIV), Years of Education (YRED), and Delinquent Record (DELREC); and (3) Division three - Age of Onset of Opiate Use(OPIATEAGE), Years of Opiate Drug Use (OPYRS), Age of Onset of Barbiturate Use (BARBAGE), Years of Barbiturate Drug Use (BARBYRS), Age of Onset of Amphetamine Use (AMPHETAGE), Years of Amphetamine Drug Use (AMPHETYRS), Age of Onset of Marijuana Use (MARJAGE), Years of Marijuana Use (MARJYRS), Age of Onset of Cocaine Use (COCAGE), Years of Cocaine Use (COCYRS), and Age of Onset of Alcohol Use (LIQUAGE), Years of Alcohol Use (LIQYRS).

TABLE 4

Total Patients Who Challenged Naltrexone, Directly (+) or Indirectly (-) (Naltrexone III)

NAS No.	Patient	Term Date	Drug Days	Miss Med	Prog. Days	URINE TEST								Remarks
						Req.	Misses	Opiate on Nal.	Opiate off Nal.	Quinine on Nal	Other	Dir. Chall.	Anecdotal Report	
009	B.C.	11/14/75	72	13	89	24	9	0	0	13	0	+	yes	Got high
019	M.C.	11/14/75	89	14	90	51	17	0	0	1	0	-	yes	Got high
020	L.F.	2/21/75	123	15	130	63	16	0	0	7	1	-	yes	Skipped often
023	S.C.	12/5/75	235	4	235	144	8	3	0	4	0	+	yes	Got high
024	P.G.	3/20/75	123	12	154	78	5	5	4	2	1	+	yes	O.D. off Naltrexone
029	H.S.	8/29/75	265	2	266	165	1	0	0	2	0	+	?	Claims placebo
032	R.M.	6/28/75	205	25	125	20	20	0	0	1	20	+	yes x 2	Not high
040	DoHo	3/7/75	43	2	97	21	4	0	0	2	0	+	yes x 3	Not high
047	E.S.	3/7/75	11	1	31	12	5	1	0	2	1	+	yes	Felt sick
050	RiSp	3/24/75	37	9	59	3	0	0	0	1	0	-	yes	Not high
054	S.P.	1/19/75	218	17	227	154	27	0	0	4	7	+	yes x 2	High; sick
056	DaHi	5/3/75	12	10	31	14	3	0	0	2	0	-	yes	
058	G.D.R.	4/25/75	4	0	7	2	1	0	0	0	0	-	yes	Medical problems
066	P.S.	1/9/76	173	12	184	92	18	11		19	11	+	yes	Hint challenge
067	W.H.		270	2	279	119	7	0	0	0		+	yes	"Sick 45 min."
070	R.N.	10/25/75	121	10	134	89	52	0	0	0	6	-	yes	Admit heroin
071	R.G.	5/7/76	239	39	295	165	42	2	0	3	15	+	yes	Admit Percodan
072	A.M.		270	4	350	118	2	2	0	3	1	+	yes	Knows placebo
073	N.H.	8/7/75	8	3	51	1	1	1	0	0	0	-	yes	
TOTALS	19		2498	194	2838	335	238	24	4	66	63	12+		
MEANS			131	10	149	70	12	—	—	—	—			

TABLE 5

Patients Who Claimed "Direct" Challenges of Naltrexone (Naltrexone III)

NAS No.	Patient	Term Date	Drug Days	Miss Med	Prog. Days	URINE TEST								Remarks
						Req	Missed	Opiate on Nal.	Opiate off Nal.	Quinine on Nal.	Other	Dir. Chall.	Anecdotal Report	
009	B.C.	11/14/74	72	13	89	24	9	0	0	13	0	+	yes	Got high
023	S.C.	12/5/75	235	4	235	144	8	3	0	4	0	+	yes	Got high
024	P.G.	3/20/75	132	12	154	78	5	5	4	2	1	+	yes	O.D. off Naltrexone
029	H.S.	3/29/75	265	2	266	165	1	0	0	2	0	+	?	Claims placebo
032	R.M.	6/28/75	205	25	216	125	20	0	0	1	20	+	yes x2	Not high
040	DoHo	3/7/75	43	2	97	21	4	0	0	2	0	+	yes x3	Not high
047	E.S.	3/7/75	11	1	31	12	5	1	0	2	1	+	yes	Felt sick
054	S.P.	11/19/75	218	17	227	154	27	0	0	4	7	+	yes x2	High; sick
066	P.S.	1/9/76	173	12	184	92	18	11		19	11	+	yes	Hint challenge
067	W.H.		270	2	279	119	7	0	0	0		+	yes	"Sick 45 min,
071	R.G.	5/7/76	239	39	295	165	42	2	0	3	15	+	yes	Admit Percodan
072	A.M.		270	4	350	118	2	2	0	3	1	+	yes	Knows placebo
TOTALS	12		2113	133	2423	1215	148	24	4	55	12	12		
MEANS			176	11	201	107	12	-	-	-	-	-		

TABLE 6

Patients Who Were Indirect Challengers of Nalrexone (Naltrexone III)

NAS No.	Patient	Term Date	Drug Days	Miss Med	Prog Days	URINE TEST								Remarks
						Req	Missed	Opiate on Nal	Opiate off Nal.	Quinine on Nal.	Other	Dir. Chall.	Anecdotal Report	
019	M.C.	1/14/75	89	14	90	51	17	0	0	1	0	-	yes	Got high
020	L.F.	2/21/75	123	15	130	63	16	0	0	7	1	-	yes	Skipped often
050	RiSp	3/24/75	37	9	59	3	0	0	0	1	0	-	yes	Not high
056	DaHi	5/3/75	12	10	31	14	3	0	0	2	0	-	yes	
058	G.D.R.	4/25/75	4	0	7	2	1	0	0	0	0	-	yes	Medical problem
070	R.N.	10/25/75	121	10	134	89	52	0	0	0	6	-	yes	Admit heroin
073	N.H.	8/7/75	8	3	51	1	1	0	0	0	0	-	yes	
TOTALS	7		464	61	502	223	90	0	0	11	7	-		
MEANS			66	8	71	31	13	-	-	-	-			

The measurements of these variables were derived from clinical data that originated from addicted individuals who can be inconsistent informants. When raw data is generated in this fashion the researcher runs the risk of losing some reliability and validity in his measurements. Since this problem is indigenous to clinical research we feel our results were no more or less affected by this bias than in comparable clinical research. No doubt there were occasions when inconsistencies appeared in the data. To correct for this bias, the variable measurements were based upon a logical predetermined standard. The measurement of the variable OPIATEAGE or age of onset of opiate use serves as a good illustration. This datum is generally found in an intake questionnaire administered to all patients each time they enter a component program of the Drug Dependence Unit. In a small city like New Haven it is not uncommon for a patient to have been a member of several programs. This results in multiple intake questionnaires for a particular patient. In a number of cases we found inconsistencies in the data that concerned this variable. The standard employed to correct this bias was to define the age of onset of opiate drugs to be the earliest date that appeared in the data. This convention failed to distort the data since all patients were treated symmetrically whenever there existed discrepancies in the data.

An SPSS (statistical packages for the social sciences) systems file was created to statistically analyze our data. The first analysis produced T-statistics for all continuously distributed variables by all discrete variables ie categories. The variable combinations analyzed were (1) SAMPLES (1,2,3,1-3, 1&2vs3)by all variables, (2) GROUP by all variables, (3) COMPD by all variables, (4) STABLIV by all variables, (6) CHALLENG by all variables, and (7) DELREC by all variables, which produced over 300 pages of output containing a considerable number of individual T-statistics. A logical process or routine was employed to break down this data. The first step consisted of identifying those particular T-tests that were consistently statistically significant for the discrete by continuous variables for all samples. By gross inspection we were able to identify four categories (discrete variables) that are: (1) GROUP, (2) COMPD, (3) STABLIV, and (4) FOLLSTAT, and four continuous variables: (1) ETOM, (2) ETOP, (3) REQURIN, and (4) NUMISS that were consistently associated with statistically significant T-tests. Our next maneuver was to assess the quality of meaningfulness of the categories by variable relationship. Two categories, COMPD and GROUP were found to be consistently related to ETOM, ETOP, and REQURIN, although the meaning of this finding fails to be very important. These variables and categories naturally overlap to the point where they lose their power to discriminate - together they measure an equivalent went. Interestingly enough FOLLSTAT and STABLIV were related to these variables but to a lesser degree. At this juncture the data appeared to suggest that: (1) no powerful relationship was extant between the continuous and discrete variables and (2) a significant relationship might be found when the categories were related to one another. To this end the other primary analysis in this

investigation was generated.

An SPSS Crosstabs procedure was employed to to reanalyee the data. Crosstabs generate two-way to N-way cross tabulations for discrete variables which can be tested for statistical significance in a number of ways including Chi-square, Phi-coefficient, and Kendall Tau-b when the matrix is NxN.

The discrete variables or categories in the second analysis consisted of GROUP, COMPD, STABLIV, FOLLSTAT, SAMPLE, and CHALLENG. The last two variables were not found to be significant in the first analysis; however they were included here since the researchers believed they were important. The variables were analyzed by a series of 1x5, 1x4, 1x3, and 1x2 Crosstabs procedures for samples one and two combined, one, two, and three combined, and one and two combined vs. thraa. This routine produced fourteen chi-squares for each of the three samples or a total of forty-two. Compared to the T-analysis, this routine produced a small quantity of data, which was broken down in a similar fashion. The break down process consisted of constructing a 4x5 matrix in which we plotted the number of times a statistically significant x^2 or Tau-b appeared in the data from the three working samples. This process produced two interesting findings that involved the variables STABLIV and FOLLSTAT (stability of living pattern and follow-up status).

As mentioned previously, FOLLSTAT was found to be related to four continuously distributed variables, ETOM, ETOP, REQURIN, NUMISS. In the second analysis this variable emerged as being very significant. The Chi-square results demonstrated that there was a systematic relationship between FOLLSTAT and the variables GROUP and COMPD, which are equivalent measurements. The variable STABLIV once again emerged as being somewhat important although the nature of its significance differed from FOLLSTAT. In the matrix distribution (4x5 plotting matrix) the variable appeared diffused. It was found to be related to GROUP, COMPD, SAMPLE, and FOLLSTAT, but failed to cluster about one or two variables the way FOLLSTAT did.

FOLLSTAT is a retrospective measure and therefore loses some of its power as a predictor by definition. Nevertheless it is one of only two variables out of thirty-five that was consistently related to program outcome. Thus we believe that it can be employed as a reference in the search for other variables that may be strongly related to program success or failure. Additional clarification is needed to determine the function STABLIV could take on as a predictor variable. Resnick (1971) also has researched a similar variable; he investigated the relationship between marital status (as defined by an ongoing, important, and consistent relationship with a woman, other than a relative) and program performance. When Resnick's sample was divided between terminators and continuing cases a T-statistic indicated that marital status could differentiate the two groups. This finding lends support to our belief that with further refinement of variable STABLIV it could prove to be an important indicator of program outcome.

In concluding we were able to eliminate a significant number of variables that have little relation to program outcome. Our data suggest that quality performance in a low intervention drug program is not related to a patient's drug history. Finally the second analysis confirms our expectation that FOLLSTAT is significantly related to GROUP or COMPD. The variable STABLIV while less significant does show some promise in the same direction.

Ongoing Research

A further study using Naltrexone is now underway in the Low Intervention Program. The study began in February 1976 and is called "Pilot Contingency Study'.'.

In essence, this protocol employs a relatively novel clinical approach to the usage of Naltrexone in dealing with opiate-dependent patients. It eliminates the difficulties inherent in double blind drug vs. placebo design. At the same time, by maximizing the importance of patients' behaviors it institutes a feedback mechanism which literally gives the patient a share of control in his own medication regime. Concretely, the patient, after a stipulated time of taking Naltrexone, is taken off Naltrexone until such time as his behavior warrants a return to antagonist drug. Such behavior includes usages of opiates and/or frequent delinquency from program requirements (attending groups and giving urines). If the individual does well in a programmatic sense, he is simply kept off Naltrexone and then eventually graduated from the program. If he is required (by his own behavior) to return to Naltrexone he is kept on it for one month and then returned to the contingencv code.

In this design, patients are randomly assigned to one of two initial treatment periods which are two months long and six months long on Naltrexone. These periods were chosen to be as different from each other as possible and also with a view to some replication of the study periods used in earlier studies.

While it is still premature to report results from this program, it can be said that as of May 20, *a* total of 13 patients had been enrolled and by random assignment, 8 had been put into the long term group and five in the short term group. One individual had already finished' "short group" (two months) and was doing well on the program without Naltrexone. Insufficient time had elapsed for other results to be produced as of the time of this writing,

Overall, the enrollment of patients, induction onto drug, and course in program have gone very well so far. Up to this point, there are no program attritions and no challenges known. Because of the early stage of development, this information is included not for analysis but rather *to* document the continuing search for a more appropriate or effective mode of administration of Naltrexone in an outpatient setting, It is felt that this is a more sophisticated and ultimately more viable approach because it recruits the motivation of the patient who is "ready" for antagonist treatment.

Conclusions

1) Three studies using Naltrexone for treating opiate-dependent patients are described. The three series varied in time of duration on medication and certain other important particulars - the first two series were "open" series and the last was a drug vs. placebo double-blind design. The series are discussed together because of certain underlying common features and because the issue of discovering a successful modality for administering Naltrexone is a central concern of this research.

2) Comprehensive medical examinations support the belief that Naltrexone is a safe substance.

3) The average patient's report leads to the conclusion that Naltrexone is a palatable substance but does cause some abdominal discomfort, usually in predisposed individuals with previous functional intestinal disorders and/or habitual use of alcohol.

4) Differential rates of retention and the possible reasons underlying them have been discussed in the three studies. One factor believed related to low retention rate in the third series, namely, challenge of narcotic antagonist, has been discussed. It is suspected that the high rate of challenge in the NAS study was related to the design of the study which employed placebo doses. The issue has not been proved, however, since only the "indirect" challengers (who could have appeared in other series as well) had a noticeably shorter duration of days on program. It is still quite possible that there was an overall downward effect on retention caused by the frequency of challenge in this series (the frequency was one-third of all patients) and the diminished confidence of all patients that resulted from the challenges.

5) Data analysis covering thirty-five variables in three categories leads to the conclusion that a number of standard areas of information gathered on patients in drug dependence programs are relatively ineffectual in discriminating the more successful from less successful patients. At the same time, two factors have been isolated which seem associated with programmatic outcome and recommendation is made for further research in this area. These factors are stability of living pattern and follow up status (with respect *to* drugs).

6) A new study now underway in the Low Intervention Program is described in an introductory way. The program is too young to provide meaningful statistical data but is, after 4 months of operation, coming along well. The program, by using contingency mechanisms which emphasize the patients' input in determining medication schedules, is designed to maximize motivational factors. It is believed that motivational factors will, of necessity, be more important in a narcotic antagonist program than in the established methods of dealing with opiate dependence. Recruitment of a sense of self determination may not only be timely but even essential in formulating effective clinical programs that offer Naltrexone.

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APPENDIX A - GLOSSARY

Division - 1: Program Variables

(CBAD) Number of Urines Positive for Barbiturate and Amphetamines
Calculated from time of client's entry to exit from program.

(CHALLENG) Challenges
If client used opiate drugs while officially taking study medication.

(COILLD) Number of Urines Positive for Other Illicit Drugs
Calculated from time of client's entry to exit from program

(COMPD) Completion of Drug
For Naltrexone I, clients took medication for 90 days. For Naltrexone II, clients took medication for 180 days. For Naltrexone III, clients took medication for 270 days.

(COMPP) Completion of Program
Clients who were officially graduated from the program.

(COPIATE) Number of Urines Positive for Opiate Drugs - Calculated from time of client s entry to exit from program.

(ETOM) Elapsed Time on Medication
Period of time in days in which the client was officially taking study medication.

(ETOP) Elapsed Time of Program
Period of time, in days, in which the client was officially logged in the program.

(FOLLSTAT) Follow-up Status (1,2,3)
This variable has three values which are 1) positive, 2) relapse to drugs, 3) unknown. A positive follow-up defined a person who did not relapse to drugs, and demonstrated acceptable social behavior. Values two and three are self-explanatory.

(GROUP) Group
Patients were classified as either being graduated/terminated in good standing or responsible drop-outs.

(NUMISS) Number of Missed Urines
Number of urines requested but not received from time of client s entry to exit from program.

(REQURIN) Required Urines
The number of urines scheduled for a patient from the day of entrance to termination from the program.

(SAMPLE) Sample (1,2,3, 1&2, 2&3,1&2 vs.3)
(1) Subject in Naltrexone I only
(2) Subject in Naltrexone II only
(3) Subject in Naltrexone III only
(1&2) Subject in Naltrexone I and II combined
(2&3) Subject in Naltrexone II and III combined
(1&2 vs. 3) Subject in Naltrexone I and II combined vs. III

Division - 2: Demographic Variables

(AGE) Age
Age at which client entered program.

(DELREC) Delinquent Record
Defined as official contact with the criminal justice system prior to clients' eighteenth birthday.

(MOINCAR) Months of Incarceration
Calculated by number of months client spent in prison, jail, or juvenile reformatory. If information was conflicting, the longest period of confinement was used.

(NUMARRST) Number of Arrests
Determined by number of client arrests, with or without a conviction.

(NUMINTRT) Number of Months in Prior Drug Treatment Programs
Calculated by assessing number of months, client spent in drug treatment programs prior to start of current program. If information was conflicting, the longest length of stay was used.

(PRDRUGTRT) Number of Prior Drug Treatment Programs
Calculated by assessing number of drug treatment programs (in or out-patient, or in jail).

(RACE) Race
White or Black. No other groups were represented in the study.

(STABLIV) Stable Living Arrangement
Scored positively if patient had satisfactory living system, usually with wife or girlfriend, perhaps with family or self. Scored neg-

atively if poorly adjusted as shown by numerous inconsistencies and/or chaotic life style.

(YRED) Years of Education
Highest grade completed by patient prior to admission.

Division - 3: Drug History Variables

(AMPHETAGE) Age of Onset of Amphetamine Use.

(AMPHETYRS) Number of years patient used Amphetamines minus any known periods of incarceration and other drug treatment.

(BARBAGE) Age of onset of Barbiturate Use.

(BARBYRS) Number of years patient used Barbiturates minus any known periods of incarceration and other drug treatment programs.

(COCAGE) Age of onset of cocaine use

(COCYRS) Number of years patient used cocaine minus any known periods of abstinence including periods of incarceration and other drug treatment programs.

(LIQUAGE) Age of onset of alcohol use.

(LIQYRS) Number of years patient used alcohol minus any known periods of abstinence including periods of incarceration and other drug treatment programs.

(MARJAGE) Age of onset of marijuana use

(MARJYRS) Number of years patient used marijuana minus any known periods of abstinence including periods of incarceration and other drug treatment programs.

(OPIATEAGE) Age of onset of opiate drug use.

(OPYRS) Number of years patient used opiate drugs minus any known periods of abstinence including periods of incarceration and other drug treatment programs.

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PATIENT RESPONSE TO NALTREXONE: ISSUES OF ACCEPTANCE, TREATMENT EFFECTS, AND FREQUENCY OF ADMINISTRATION

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Charles Savage, M.D.

INTRODUCTION

The experiences concerning naltrexone to be presented in this paper represent a subset of the National Academy of Sciences (NAS) collaborative study. Thirty-eight subjects were inducted to naltrexone or placebo-in a double-blind fashion for a nine-month trial. Administration of the drugs was for the initial two months six days a week, and thereafter on a thrice weekly schedule. Extensive laboratory and medical information was obtained for assurance that naltrexone was a relatively safe compound. Urine testing, demographic changes and ancillary treatment measures were continually monitored to assess the effectiveness of naltrexone in a drug rehabilitation setting.

The pertinent issues that this paper addresses concerning naltrexone are: its acceptance; treatment effects; and the frequency for administering naltrexone.

SUBJECT CHARACTERISTICS

Table 1 illustrates the characteristics of volunteer subjects participating in the National Academy of Sciences (NAS) Pilot Study. These characteristics are consistent with those obtained in various other studies at this clinic. Subjects are generally unmarried, in their middle to late twenties, educationally at the junior high school level, black, and of lower economic status. Prior experience in drug rehabilitation is minimal, usually consisting in one previous treatment for a duration of four months. Since subjects are legally classified as parolees or probationers, all have criminal records with an average of nine previous arrests.

ACCEPTANCE

The issue of the acceptability of naltrexone

in particular and the narcotic antagonist concept in general has always been paramount. In view of the context in which naltrexone has been tested, serious questioning must take place before the scientific community accepts definitive results on this issue. The recruitment efforts of the Narcotic Clinic indicate that of 99 eligible candidates, 38 consented and began antagonist treatment. This rejection rate does not necessarily imply that 62% of the population finds naltrexone to be an unacceptable method of treatment. On the contrary, verbal reports and follow-up behaviors illustrate in this setting that some prospective subjects disavow any tendency to achieve abstinence. Others find the required testing procedures "harassing," and are quite honestly "scared away" from the drug. While responsible investigators realize the necessity and appropriateness for rigorous medical testing and conforms to protocols, let no one be deluded in thinking that within the strict adherence to them, can the true acceptability of any compound be judged objectively. At best, one can only judge the acceptability of the research and secondarily the acceptance of the drug by the active participants.

The experience from our testing site is that study patients report only minimal disadvantages to the medications under study. These reports are those primarily of taste and some mild stomach discomfort during the initiation phase to the drug.

Using length of treatment as one indicator of acceptance, naltrexone subjects' participation in the NAS Study was for 80.9 days and placebo counterparts for 92.1 days. While this duration appears to favor placebo subjects, their length of treatment is confounded by subjects using heroin for a period of two to four weeks. This drug taking behavior is not an option usually available to the naltrexone subjects. Therefore, it is reasonable to say that naltrexone in this study is comparable to placebo as an acceptable agent.

TREATMENT EFFECTS

Table 2 illustrates the treatment outcome for the thirty-eight subjects treated in this study. As is indicated, four subjects completed the full nine months of study. This category was evenly divided between the naltrexone and placebo groups.

Five subjects terminated for reasons of side-effects and all were taking naltrexone. Three of these subjects complained of symptoms resembling mild heroin withdrawal. While precautions were instituted to guard against initiating subject concurrently taking heroin, urine surveillance records indicate that each of these subjects had taken heroin prior to naltrexone ingestion. These men experienced the normal physiological reaction to an antagonist drug, hence, their complaints cannot be considered side effects. Of the remaining two terminated subjects, one reported the symptom of nausea and the other of constipation and stomach discomfort.

One placebo subject was discontinued as a result of an abnormality present on repeated physical examinations. This subject experienced a significant weight loss and since he

TABLE 1

Sample Characteristics

	Naltrexone (N=19)	Placebo (N=19)
Age	26.05	26.00
Marital Status		
Single	12	14
Married	4	4
Divorced	3	1
Education		
Attended Grade School	1	5
Completed Grade School	4	3
Attended High School	13	10
Completed High School	1	1
Previous Drug Treatment		
Total Number ($\bar{X}$)	1.3	.8
Months ($\bar{X}$)	4.9	3.9
Legal		
Arrests ($\bar{X}$)	9.3	8.7
Convictions ($\bar{X}$)	3.4	3.7

TABLE 2

Duration of Treatment (Days) By Termination Classification (N=38)

	Naltrexone		Placebo	
	N	$\bar{X}$	N	$\bar{X}$
Successful Completion of Study	2	268	2	268
Absences	5	73.8	6	25.3
Readdiction	0	--	7	96.85
Symptom Side Effects	5*	6.4	0	--
Abnormal Physical Finding	0	--	1	81.0
All Other Reasons	7	85.9	3	101.3
Total Length of Treatment	19	80.9	19	92.1

* Three subjects complained of mild withdrawal syndrome. Not considered true side effect due to heroin use prior to initial dose of naltrexone.

was not on active medication, this finding is not attributable to the drug.

Subjects terminating under the broad category, "all other reasons," include a myriad of reasons not related to the medications under study although more naltrexone subjects gave this reason. This heading consists of incarceration, transfer to another program closer to residence, and often because the subject indicated that he could "make it on his own" without the aid of any medication. Analyses differentiating this category have not been completed since reliance on follow-up data is indicated to document post-medication behaviors. At present cursory examination of this category does not reveal startling trends of significance.

The greatest proportion of subjects falls under the "absences" category for reason of termination. While the number of subjects does not greatly differ between the two treatment groups (Naltrexone 5; Placebo 6), the duration of treatment before the absences occur is noteworthy. Clearly, in reference to absconders only, naltrexone patients remain in the research regimen three **times** longer than their placebo counterparts. The occurrence of naltrexone patients remaining in treatment for this duration is particularly interesting upon comparison with placebo subjects who became readdicted. Note is made of this comparison for it exemplifies a consistent pattern in other studies at this clinic (Kurland, Hanlon, and McCabe, 1974) and offers a viable explanation for the absences of naltrexone patients. The inference from this comparison is that naltrexone subjects incur a greater susceptability to heroin use after two months of treatment, and finding that reinforcement is prevented, absent themselves from further naltrexone treatment. Placebo subjects experience this same phenomenon but since pleasure is obtained, continue to attend the clinic and simultaneously use heroin. The research protocol allows for a two- to four-week pattern of heroin use before termination for reason of evidence of possible readdiction. Hence, the placebo subjects' duration of treatment is greater allowing for continued heroin use.

Further examination for the cause of this heroin use after two months of treatment was conducted. Possibly the frequency with which the study medication was administered contributed to this finding. The investigators note that a sharp increase in heroin use is coincidental with a transition from six days/week to a three days/week administration schedule. To examine this inference, a comparison was made between the thirty-four subjects terminating in the NAS Study (Study 1) and nineteen subjects terminated from a more recent naltrexone/placebo study (Study 2) in which subjects immediately receive medication three times a week after a one-week induction schedule. The results of this gross comparison indicate Study 1 terminated subjects' duration of treatment was 65.20 days and Study 2 terminated patients' was 31.05 days. The suggestion that subjects may remain in treatment longer when daily clinic attendance is required may counter the utility of naltrexone which blocks the effects of heroin for 48-72 hours. The obvious benefits to the client and clinic when employing a thrice-weekly schedule are many. However, these benefits may need to be reevaluated if continued treatment participation (a general indicator of successful progress) is maximized in a more freauent administration schedule. This finding, as mentioned, is the result of a gross analysis to glean possible causes for explaining drug use after two months of antagonist treatment.

At this early phase of analyzing the data from the NAS Study other causes may be present but not as yet evident. The mentioned inference, however, exhibits one facet of many questions yet to be asked concerning the utility and effectiveness of naltrexone.

ACKNOWLEDGMENT

This work is supported by Grant No. DA00415 from the National Institute on Drug Abuse.

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NALTREXONE IN METHADONE MAINTENANCE PATIENTS ELECTING TO BECOME "DRUG FREE"

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This study examined the role of Naltrexone in Methadone maintenance patients who wished to become drug free. At the beginning of the study the Methadone maintenance program had approximately 300 patients, all male, the majority of whom had been on the program for over two years. The ethnic breakdown was roughly 1/3 each for white, black and Mexican-American. All patients who expressed the wish to become drug free between July 1974 and October 1975, who were receiving a dose of 50 mg. or less and had been on the program six months or longer were logged regardless of their interest in Naltrexone. Patients who were detoxifying on a disciplinary basis were excluded. All patients were informed of the availability of Naltrexone, its action as an antagonist and potential usefulness and the double-blind nature of the study; 104 patients were logged, 15 were ineligible for the study because of medical, alcohol or psychiatric problems; 28 did not complete detoxification (incomplete group); 61 patients co letely detoxified from Methadone and 32 of these elected to enter the study and took at least one dose of study medication (study group). Those who detoxified but did not start study medication are called refusers. In terms of age and time on Methadone maintenance, these groups were similar (see Fig. 1).

Many reasons were given for the decision to detoxify. Most often they involved a wish to be drug free and this was associated with a wish to be free of the restrictions imposed by Methadone maintenance, such as regular clinic attendance, difficulty with vacations, etc., and a wish to disassociate themselves from the addict identity. They expressed the belief or wish that thev could "make it on their own." Some had family pressures to--detoxify. Those who were most adamant that they could make it on their own and who gave this as their reason for detoxification tended to be the least interested in Naltrexone. Those who were less certain of their ability to "make it" and who expressed some fear of relinquishing the security and qualitative improvement in their lives (stability of work and personal relations, difficulties with law enforcement) that they felt Methadone maintenance had allowed them to attain, were most

interested in Naltrexone. The availability of Naltrexone was a factor in tipping the decision of this group to detoxify. Some of this group expressed interest but objected to the double-blind because it meant giving up the known security of Methadone maintenance for only the possibility of an effective agent. These patients seemed keenly aware of their vulnerability to heroin use. Generally those patients who expressed the fear of their own vulnerability were most interested in Naltrexone and elected to take it after their detoxification. The availability of Naltrexone also seemed to be a factor in their continuing their detoxification at points where they experienced difficulty. However, these factors did not significantly predict who did complete their detoxification.

Detoxification from Methadone is a difficult process involving physiologic and psychological stress. Almost all patients experienced a high degree of anxiety during their detoxification and it was often difficult to determine clinically what symptoms were due to anxiety and what were due to withdrawal. A variety of detoxification programs was utilized, The main variations were: (1) patient controlled decreases, (2) an 8-week fixed schedule from 50 mg, that was known to the patient, and (3) a blind 8-week fixed schedule. Generally, this was conducted on an outpatient basis, Patients did have the option of entering the hospital for the final phase of their detoxification, and some patients elected to do this. In addition, supplemental medications were used symptomatically--the tricyclic/Phenothiazine combination--Triavil, Valium, Dalmane and Darvon. Patients demonstrated tremendous variability in the course of their detoxification ranging from a very smooth course with negligible difficulties to wishing to stop after their first decrease in dosage. The different detoxification schedules and hospitalization did not seem to affect the course of the detoxification as much as the resources of the patient, the stability of their environment and their relationships with the staff of the program. The availiabity of Naltrexone did encourage some patients to continue or resume their detoxification after experiencing difficulties. However, the risk of receiving a placebo often had the opposite effect. It is our impression that if the study had been open, the availability of Naltrexone would have played a greater role in motivating patients to continue their detoxification.

A number of patients who declined to start study medication after their detoxification feeling they "could make it on their own," subsequently returned after having used heroin and requested Naltrexone instead of Methadone maintenance. Some patients, who had only a few doses of study medication and then dropped out, also returned in this manner but were not restarted because of the protocol. The return experience is the most impressive observation we have made. Apparently the experience of detoxified patients in finding themselves vulnerable to using heroin seemed to give them a more realistic view of their situation and made Naltrexone valuable in their eyes. Their preference at that point for Naltrexone rather than Methadone maintenance is quite significant. The inability to use Naltrexone intermittently in such patients was an unfortunate handicap imposed by the protocol. Had we been able to restart patients, many who dropped out would have dropped back in. Fran a clinical standpoint, this is significant in that we should expect patients to stop and start their medication and it is no more reflective of the medications acceptability or effectiveness than antihypertensive agents which patients start and stop (in part because like our patients they have no acute symptoms to motivate strict usage of medication). A further practical observation relates to the starting dose. We followed the induction schedule in our protocol beginning with 10 mg. and doubling the dose daily for the next four days. However, many of our patients tested the effect during the first two days, even though they were told that they did not receive a full blocking dose. Many of these patients terminated the study at this point, feeling that the medication was ineffective or that they had received a placebo. We feel that an initial dose of 30-50 mg. would provide a moderate blockade for 24 hours and would be useful in retaining patients--even at the risk of inducing side effects.

This issue is exemplified by the data that almost 1/3 of our patients terminated during the first week, and a second third bv the end of the first month (see Fig. 2).

Safety. We had few incidents suggestive of adverse reactions. One patient did experience a psychotic depressive reaction after three months of study medication. However, after reviewing the course of his illness, the precipitating social and psychological stresses and a past history of a similar episode manv years prior, we concluded that this was probably not related to the study medication. A number of patients did complain of gastrointestinal symptoms, particularly an "upset stomach" during the first two weeks. This was usually relieved by antacids and was transient. One patient did terminate himself because of a persistent upset stomach. One patient who detoxified rapidly from 80 mg. in less than two months became highly agitated at the end of his detoxification. He continued to be extremely agitated after starting study

medication. After two weeks, study medication was discontinued, but the agitation remained. Subsequently, he was restarted on Methadone with a diminution of his agitation. Although it was believed that his agitation was due to his rapid detoxification, other factors including legal and social problems were present.

The major reason for early termination (see Tab. 1) was readdiction and/or a request to return to Methadone maintenance. Eleven subjects fall into this group. Their time on study medication ranged between one day and eight months. Generally these patients briefly discontinued their study medication and became readdicted. Subsequently they either directly requested a return to Methadone maintenance or could not be detoxified in a resonable time in order to restart study medication. Due to the uncertainty of the double-blind, both staff and patients tended to reinstate Methadone maintenance more quickly than had this been an open study. Two patients used heroin daily for two or more weeks despite acknowledging that they could not get an effect. They elected to return to Methadone maintenance because of the legal, financial and social problems of continued herion use. One patient attempted to overcome the blockade by titrating himself with sequential injections of "half spoons;" after the seventh half spoon he experienced a mild heroin effect and with the next half spoon a full effect. He then requested Methadone maintenance. As of May 1, 1976, over half of the patients who began study medication returned to Methadone maintenance (see Fig. 3). This included one patient who completed the full nine months of study medication without a dirty urine but who became readdicted to heroin subsequent to ending the study. More significantly, a follow-up questionnaire indicated that of the patients who returned to Methadone maintenance, two out of three would return to Naltrexone if it were available. Our continuation study will tell us if they actually do.

Future Outlook. We are encouraged by our experience with Naltrexone and plan to continue our investigation. Although it is not an alternative to Methadone maintenance for all patients, it does seem to be an attractive next step for many patients who have stabilized their life style on Methadone maintenance but who are reluctant to jeopardize their gains by detoxification and fear their vulnerability to heroin use. There has also been a concomitant effect on the staff of our Methadone maintenance program. Prior to the availability of Naltrexone, there was much discussion of the issue of detoxification and the question of how long should patients be on Methadone maintenance. However, most staff rarely

TABLE 1

Primary Reason for Early Termination

Abnormal physical/psychiatric findings after study medications

1. (Psychotic depression)

Symptom Side Effects: 4

Speeded up)
Sleepy)
Agitation) One each
Upset stomach)

Illness: 1

Polycystic kidneys -- urinary tract infection.

Evidence of Readdiction and/or request for Methadone maintenance: 11

Disciplinary discharge: 1

(Stealing on grounds)

2 weeks unexcused absence: 3

Patient feels can make it on own: 5

Other -- traveling to clonic interfered with work: 1

Completed: 3

On study meds: 2

FIGURE 1

Time on Methadone Maintenance in Months at Log

	6 - 12	13-24	>24	N	Mean
S	7	9	16	32	25.3
R	8	11	10	29	20.75
I	7	8	13	28	23.44

Age at Time of Log

	< 25	25-29	30-34	35-39	>40	N	Mean
S		5	8	10	9	32	36.32
R	5	11	5	2	6	29	30.00
I		8	9	3	8	28	34.25

S = Study Group
R = Refuser Group
I = Incomplete Group

FIGURE 2

Total Time on Study Medication at Termination (in days)

1-7	8-30	31-90	91-180	>180	Complete 9 months
9	9	5	3	1	3

Two patients still active

FIGURE 3

Followup Status of Patients Who Started Study Medication as of May 1, 1976

MM	NC	Off	Jail	On Study Medication
17	6	55	2	2

MM = Methadone Maintenance
NC = No contract >3 months
Off = No maintenance medications

initiated discussions or strongly supported their patient's efforts to detoxify because of their own sense of futility and feeling they had little to offer these patients. With the advent of Naltrexone, there was a shift in this attitude with the staff feeling that they now had an effective agent to offer their patients after Methadone. This helped them to initiate exploratory discussions of detoxification with patients and to be much more supportive during detoxification rather than subtly influencing the patient to return to Methadone maintenance at the first signs of any difficulty.

Conclusion. Although our experience with Naltrexone as a follow-up modality to Methadone maintenance is still in an early stage and difficult to evaluate, we are encouraged by our experience with the NAS study. This is particularly important considering the high relapse rate following detoxification from Methadone maintenance. It is our experience that patients take Naltrexone not merely because of the physiologic blockade produced but because it is our extension of the program. In the past most of our Methadone maintenance patients who detoxified quickly severed their participation in the program despite encouragement to remain active. This allowed the patients little or no opportunity to deal with the emotional factors of being drug free and the prolonged abstinence syndrome often seen in Methadone maintenance with the support of the program. Contact might be subsequently reestablished only after readdiction to heroin occurred and treatment by Methadone maintenance would be reinstituted. Naltrexone gives patients a reason to continue their active participation during this transition phase. Staff as well, view Naltrexone as adding to their own credibility with detoxified Methadone maintenance patients and motivates them to be actively involved with their patient during detoxification and their transition to Naltrexone. Thus Naltrexone works to enhance the overall rehabilitation program and expand its effectiveness to both staff and patients. Even though we had a very high dropout rate, the retention of the study group in the overall program was many times greater than the patients who detoxified but refused Naltrexone. Thus Naltrexone does seem promising as a transition treatment for Methadone maintenance patients electing to become drug free. In this study, the decision to take study medication was based on self-selection. Future work will also include attempts to define what characterizes patients who are most likely to benefit from Naltrexone as a transition modality.

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COMMENTS AND FINDINGS FROM A NALTREXONE DOUBLE BLIND STUDY

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PATIENT CHARACTERISTICS AND OUTREACH

Essentially three groups of patients emerged from the Lafayette Clinic naltrexone double-blind study. The first group was comprised of those who came to the program via advertisement or referral and decided it was not what they wanted. Hence the only available data for these individuals consists of basic demographic information collected on an intake face sheet. The second group was comprised of patients who received methadone but did not receive study medication. Since these individuals were involved in treatment much longer, extensive social and psychological data were also collected. The third group was comprised of any patients receiving study medication. The same data collected on the second group was also collected on these patients.

An attempt was made to determine whether there were any characteristics which would differentiate those receiving methadone as opposed to those who also received study medication. Because of the minimal data available on those who were only seen at intake, there were no comparisons done with this group. The methadone and study groups were similar in terms of analyses which compared 45 MMPI scales as well as two-point code profile analyses. The social maladiustment scale which has items indicating shyness and minimal social involvement was found to be higher for the methadone group ($p<.05$). However, it should be noted that the T scores for both groups were well within the normal range, T score <60.

The average MMPI profiles were virtually identical characterological profiles with elevations on the Depression and Psychopathic deviate scales. Comparisons were also made between the obvious and subtle scales for

both groups. These scales include the depression, hysteria, psychopathic deviate, paranoia, and mania scales. For both groups the obvious scales were elevated above the subtle scales, but still within the normal range. These findings would indicate that both groups have a tendency to exaggerate their symptoms at the time of intake. These findings also reflect the relative lack of sophistication of most of the patients seen.

Demographic and social history variables were also compared. The naltrexone patients were significantly older ($p<.05$) than the methadone patients. Although no other demographic variables were significantly different, it was found that there were more blacks and more single individuals in the naltrexone group.

Three social history variables were significantly different ($p<.05$) between the groups. The methadone patients had more socially deviant fathers and siblings. More of the naltrexone patients had both parents using alcohol, and more mothers and fathers using either alcohol or drugs. It was also found that more of the methadone patients lived with other drug abusers. These other abusers were in many instances the wives of the patients. Our past experience has found drug abuse by the spouse to be a very important prognostic indicator. The more basic prognostic indicator may however, be simply whether the patient currently lives with any drug abuser. Although no other social history variables were significantly different between groups, it appears that overall the naltrexone patients look better on a variety of dimensions. They appear to have had less criminal involvement. There are thus fewer naltrexone patients on probation. More of the naltrexone patients were veterans. The source of support for the groups indicates that more of the naltrexone patients are employed and receive their support from family or friends. They also receive less support from public assistance , spouse, or illegal activities.

Both groups were scaled on the following family dynamics variables: Child and Parent Roles, Family Scapegoat, Symbiotic Relationships, Familial Communication, Family Cooperation, Discipline of Children, Presence of a Significant Role Model, Sibling Rivalry, Peer Group Influence, and Family Leadership. Although a double blind rating on these scales was not used for the two groups, there were nonetheless no significant differences found between the groups. Both groups generally had poor family interrelationships. The most striking deficiencies were that both groups evidence very dysfunctional discipline from parents, and very poor communication among family members.

CURRENT USE OF NALTREXONE

Since the double blind study had discontinued intake, we have taken another approach which we believe may be more fruitful. First, we have attempted to service the industrially employed addict by offering multiple modalities. These modalities include either methadone, L-Methadylacetate, naltrexone, a Dextromethorphan hydrobromide placebo. Patients in this design are assigned to either methadone maintenance or an opiate free condition based upon their MMPI, work history, psychiatric ratings, psychological ratings, motivational ratings, extent of family problems, and extent of their criminal involvement. After atients are assigned to either of these tracks, they are randomly assigned within the tracks to receive either methadone or LAAM in the maintenance track or naltrexone or a dextro-methorphan hydrobromide placebo in the other track. In this way, we hope to differentiate between those who may benefit most from one form of treatment versus the other.

Patients who are on probation or parole have been shown to do better in treatment than those not faced with such contingencies. In a similar manner, we believe that patients whose source of income is contingent upon elimination of a substance abuse problem will also do better in treatment. We thus see the industrially employed addict as being more suitable for antagonist or opiate free treatment.

SAFETY

The Detroit Naltrexone Program monitored the physical characteristics of its patients quite carefully. In some patients, both systolic and diastolic blood pressure increases were noted. Some of these increases may have been due to causes other than naltrexone. Among the possible causes were:

1) use of other substances
2) physical problems unrelated to naltrexone
3) anxiety precipitated by detoxification from methadone
4) anxiety precipitated by the informed consent

The question of actual cause, however, still

remains open. Analyses of the blood pressure records of the naltrexone and placebo patients may be helpful. However, there may be relatively few patients who took the naltrexone long enough to make final judgements possible.

Many of the Detroit patients admitted abuse of other substances including alcohol, barbiturates and amphetamines, while taking the study medication. The mixture of other medications with naltrexone may have been responsible for some of the side effects reported. Future research should clarify the effects of such mixtures.

Since studies thus far have not analyzed the effects on women, the treatment of husband and wife abusers has been made more difficult When the safety of naltrexone is assured, the clinical utility should thus increase dramatically.

PROBLEMS ENCOUNTERED IN DOUBLE BLIND STUDY

The naltrexone program initially intended to treat referrals from the criminal justice system who were either on probation or parole. Because of legal questions raised about the use of a research drug with these patients, this approach had to be abandoned. The staff of the Substance Abuse Department then decided to make outreach efforts among patients who had been receiving methadone for a prolonged period (6 months) and who were now ready for an alternative treatment which would eventually leave them opiate free. Contacts were made within the Detroit metropolitan area with directors of various methadone treatment centers. Although these individuals appeared receptive, their help was minimal. One of the primary reasons for this was because funding of methadone programs is directly related to patient census. At the time that our program sought patients, the methadone programs were having difficulty keeping their patient censuses high enough to maintain funding. Methadone programs therefore wished to keep as many patients as possible involved in their respective programs.

Since Lafayette Clinic is located in the central area of Detroit, most of the referrals concerning substance abuse are made by programs serving a primarily black population. The black community is well aware of Lafayette Clinic's focus on psychiatric research. The community is therefore somewhat suspicious of treatment of community members with a research drug such as naltrexone. It is therefore possible that this may have hindered referrals to the naltrexone research program.

Efforts were also made to contact counselors, social workers, and other therapists who had day to day contact with the patients. This succeeded in producing more referrals but the number was still relatively small. Furthermore, it became apparent that the patients being referred to us were those who were causing the greatest problems in their former programs. The Detroit Naltrexone Program was thus hampered by problems in getting suitable referrals.

The initial design of the study was double blind. This raised a variety of problems. Among these were:

1) The patients tested their medication and, hence, were often the only ones to know what they received.

2) Patients who found they were not receiving naltrexone saw no point in continuing the program.

3) There was some attrition when patients were informed (via informed consent) that they might not receive naltrexone at all.

4) The informed consent which made clear all possible risks to be encountered, also may have had a tendency to limit program participation.

Thus far we have only made a beginning in determining factors which may prognosticate longer involvement in antagonist treatment. It is clear that all patients are not suitable for treatment with antagonists. The future objective must therefore be to determine more conclusively which patients are most suitable for this treatment.

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FACTORS INFLUENCING SUCCESS IN AN ANTAGONISTIC TREATMENT PROGRAM

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BACKGROUND

Broad efforts have been made over the past three years to evaluate the efficacy and safety of antagonist drugs in the treatment of heroin addiction. Such treatment is predicated on Wikler's hypothesis that drug-seeking behavior is conditioned. Hopefully, the use of an antagonist will prevent the opiate "high", leave the drug-seeking behavior unreinforced and thus lead to the extinction of the habit.

Efforts with Cyclazocine demonstrated it to be a toxicologically safe blocking agent to the opiate "high" but producing sufficiently noxious side effects as to preclude its ready acceptance by the treatment population. Consequently, other antagonists were explored; in particular, early pilot studies of Naltrexone indicated it to be a safe blocking agent - apparently without side-effects.

Based on this and other evidence, a large double-bind study of Naltrexone was organized. Three complementary protocols were deployed so as to provide a wide sprectrum of sociodemographic data.

Protocol 1, implemented in St. Louis, called for the systematic induction of street addicts onto study medication. Forty-two patients volunteered for the program. They were given an explanation, accepted on a closed ward, detoxified on Methadone and received a complete medical and psychological work-up including: complete physical, SMA-12, hematology, urinalysis, Australian Antigen, Chest X-Ray, EKG, mental status, psychiatric, neurological etc. While on the ward, each met with the screening committee, signed the informed consent and was assigned to study medication (blind).

Of those volunteering, two were rejected for medical reasons; one refused his random assignment; the reminder were placed on study medication in accordance with the protocol. After complete induction and briefing, each patient was released into the community where he was supported by systematic counseling, vocational evaluation, training and placement.

DESCRIPTION OF TREATMENT POPULATION

During the research period, approximately 400 clients passed through the St. Louis Central Intake Unit. Of these, 267 were logged and received an explanation of Naltrexone. Forty-two accepted the terms of the protocol and were inducted. As part of the Intake procedures, a comprehensive social history was taken. From such histories, data was extracted on age, education, marital status, rate of employment, rate of criminal activity and occupational status. These data formed both the basis for a population description and a baseline for future compasrlson.

Upon intake, the following population statistics were gathered:

(1) Age - the man was 24.6 with an interquartile range of 21.21 t0 27.00.

(2) Education - the mean grade achievement was 10.975 with an interquartile range of 9.8 to 12.125.

(3) Marital Status - twenty-one reported as never being married; one had been married but separated; two were divorced; sixteen were married end/or enjoyed a commmon-law status.

(4) Occupatlonal Status - two reported a job status of professional; four as skilled laborers; four as semi-skilled laborers andtwenty-two as common laborers.

(5) Rate of Employment - over the two-year period immediately preceding intake. four reported as 100% employed; three as 75% employed; ten as 50% employed; eleven as 25 employed and twelve as totally unemployed.

(6) Rate of Criminal Activity - over the two years preceding Intake, each study client was classified-on the basis of his criminal involvement; one reported no criminal activity; four indicated "an occasional misdemeanor"; fourteen admitted to occasional felonies; ten reported moderate amounts of criminal activity and eleven indicated a long and heavy involvement in crime.

As a rule, the St. Louis clients were young black males under legal pressure, with a history of one or more previous treatment admissions. Typlcally, each professed a desire to really "get it together", to get a job, to get back with their families etc. Most appearedtobe fromabroken family of origin with which they still maintained ties, usually with a mother. On hearing about the antagonist drug effects, they indicated their satisfaction with the concept, made plans for rehabilitation but seemed unable to carry out their plans,belng constantly distracted by the field.

PROGRAM EXPERIENCE AND SUGGESTIONS FOR THE USE OF NALTREXONE

As long as our patients were on the ward, they appeared to maintain positive attitudes toward medication but upon returning to the community, patients appeared to experience a gradual deterioration in treatment motivation; first missing medication upon occasion, then not coming for some time and,finally,dropping from treatment. In some cases our treatment staff were able to coax them back - usually not. Clients residing with families appeared to maintain motivation longer than others. It appeared particularly productive for the treatment staff to interact with family members, asking them to encourage the client to take the medication. Contrastingly, patients were often placed under pressure by wives and/or girl friends to "hurry on home - you can make it". Such patients Invariably lost motivation more rapidly.

It would appear that the availability of a strong compatible reference group is crucial in the use of Naltrexone; coming daily under the influence of such a group ensures the taking of medication. In the absence of some such dynamics, Naltrexone therapy simply won't work.

Early in the program, patients tended to misbehave on the ward,notreturnlngontime from week-end passes, not getting up on time and failing to maintain an acceptable level of ward orderliness and cleanliness. Concomitantly, there were numerous quarrels among the patients and also between staff and patients. Often bizarre and unreasonable demends were made of the staff.

The staff met to consider the above problems. After careful consideration, it was concluded that these behaviors were a function of the following:

(1) Overidentification with patients by our ex-addict counselors.

(2) A lack of recreational activity on the ward.

(3) Failure to cultivate patients' responsibility.

Staff training sessions were conducted. To develop a feeling of professionalism, a recreational specialist was assigned to the ward; systematic efforts were made to develop ward government procedures in which clients were assigned significant roles and responsibilities; whereupon, the above problems were largely obviated.

Six to nine months after discharge, each patient was contacted. Eight were drug free. previous research by the St. Louis team found program retention to be related to education, marital status, employment, occupational status etc. Accordingly, on similar variables, the eight drug-free clients were compared to our other clients. As expected, the eight successful clients were better educated, displayed higher status occupations, higher rates of emloyment. lesser criminal activity. These data are displayed in Tables 1, 2, 3 and 4.

Having a relatively high level of education, a relatively high occupational status, relatively high previous rate of employment are each good indicators of successful rehabilitation. Having a relatively high rate of previous criminal behavior or relatively low levels on the above variables, are probably contraindicators of success on Naltrexone.

Our experience suggests that therapy and motivation are enhanced when:

(1) Treatment staff maintain a posture sufficiently close as to be accepted as a role model but sufficiently far as to cause a mild discomfort or inadequacy feeling.

(2) Clients are encouraged to accept responsibility and make decisions in their own therapy.

(3) Staff maintains rapport, not only with clients but also with persons likely to influence clients.

(4) Positive reinforcement of desirable social behavior is used rather than negative reinforcement for adverse behavior.

CLINICAL AND TOXICOLOGICAL IMPRESSIONS

During the study, especially during induction, vital signs, blood chemistry, hematology and EKG were carefully monitored. No apparent medical problem was foundtobe associated with study medication. There were, however, some side-effects. Such side-effects were usually mild and transitory in nature, consisting of such things as drowsiness, headaches, sweating, stomach distress, blurring of vision etc. It appears reasonable to conclude that Naltrexone is a safe blocking agent to the opiate "high" - acting up to 72 hours - occasionally producing mild, transitory side-effects as indicated above. (This conclusion is consistent with the findings of an earlier pilot study and of our present open study.)

PROSPECTS FOR FUTURE RESEARCH

A certain amount of pessimism is generated when one reviews our collective rehabilitative experience over the last decade. Treatment success has been very limited. Rehabilitation requires a change in behavior. Such behavioral changes are seemingly a function of the field and, as such, are not sufficiently controllable as to make such behavioral changes a planned phenomenon.

Naltrexone, in and of itself, cannot change behavior, but it can serve as a buffer against the reinforcing properties of the opiate 'high!' Taking Naltrexone,an individual can go about his dally tasks, secure in the knowledge that he cannot get high. As a consequence, he will not be tempted take drugs. Being in such a position provides respite from the drug-scene pressures. Hopefully, such conditions permit the individual to learn new attitudes, form new associations, re-establish social creditability and, in general, reconstitute his identity. The greater the level of previous functioning, the better will be the chance of rehabilitation. Obviously, some of the indicators of success are such things as education, marital status, occupational status, previous rate of employment, lack of previous criminal activity etc. By way of generalization, higher levels of socialization are indicative of more sophisticated social skills which, in turn, are more likely to facilitate adjustment.

But having these good qualities will not of itself assure successful rehabilitation. Additionally, the client requires a wholesome reference group, wholesome recreational alternatives, gainful employment, an acceptable niche in the fabric of society. For rehabilitation, Naltrexone and personal skills provide the potentiality, but the field itself must extend a helping hand and the opportunity. Society must make a place for the ex-addict. Falllng to do so foredooms rehabilitative efforts to failure.

Antagonist drugs, Naltexone in particular, have been demonstrated to be toxicologically safe, posing no greater risks than are inherent in other chemotherapies. Unfortunately, the question of efficacy is not nearly as clear. Before this question can be answered, several other ingredients are needed:

A. Clear, easily applicable criteria are needed as indicators and/or contraindicators for selecting or rejecting Naltrexone. We might undertake a comprehensive regression study, using a clearly defined measure of treatment success as the dependent variable and a large battery of social and psychological variables as independent variables. Arising from this would be a set of weights. Application of those weights would greatly enhance the effectiveness of treatment decision.

B. Community based linkages are needed to assure broader citizen input to treatment decision; such participation will facilitate re-acceptance of the ex-addict. Careful plans for bringing about change in societal attitude is required. Skilled change agents should be recruited to the task. Inter-institutional cooperation on treatment decision should be fostered; especially, between the judicial system and the drug-treatment facilities.

C. Treatment is often thwarted by a tendency for staff to over-identify with the drug-taking culture. Research is needed to isolate the contraproductive attitudes of staff. Having accomplished such research, systematic education and attitude change can be undertaken.

D. Doubtless there are numerous potential clients who are locked into their anti-social attitudes because of their abject dependence on interaction within their deviant culture. If we are to attract them into treatment, we must find a way of getting in touch with them.

Systems people, sociologists and anthropologists may be asked to study the primary message systems of the drug culture so as to develop some means of direct communication. At present, the deviant communication svstem is relatively closed in reference to the larger society.

E. As a condition of probation and parole, the Criminal Justice System might ask some of its charges to participate in further research. Such legal pressure would function as a means of "forced compliance" holding the client in the situation so that relearning would take place.

As a final observation - since the effectiveness of Naltrexone depends on the quality of ancillary services, it is unreasonable to evaluate it on the basis of urinalysis, criminality, educational Improvements, individual support etc. If (as we have written) we wish to test the efficacy of Naltrexone as a useful adjunct to a good treatment program,how can we do so if one or more fundamental ingredients of rehabilitation are generally absent from our social context? It is the contention of this paper that we (at least in St. Louis) are incapable of testing the usefulness of Naltrexone unless we address issues raised in A, B, C, D and E. Further, in order to provide the field for such research, Naltrexone, which has been demonstrated as toxicologically safe, should be made available to the general addict population, as a therapeutic tool for the use by physicians in the field.

TABLE 1

LEVEL OF EDUCATIONAL ACHIEVEMENT

	X	SD	N	
DRUG-FREE	12.06	2.54	8	t = 1.84 df = 37
OTHERS	10.79	1.47	31	p .05

TABLE 2

OCCUPATIONAL STATUS

CATEGORIES *	A	B	C	D
DRUG-FREE	2 - 25%	1 - 38%	1 - 50%	4 - 100%
OTHERS	0 - 0%	3 - 13%	3 - 25%	18 - 100%

* *Under each category (A, B, C, D), for each population is listed; the number of clients and the cumulative percentage through that category. Categories are described as: A - Professional, B - Skilled, C - Semi-skilled and D - Common labor.*

TABLE 3

PRETREATMENT RATE OF EMPLOYMENT

CATEGORIES *	A	B	C	D	E
DRUG-FREE	2 - 25%	2 - 50%	1 - 63%	2 - 88%	1 - 100%
OTHERS	3 - 9%	1 - 13%	9 - 41%	9 - 69%	10 - 100%

Categories A, B, C, D and E list respectively (for each population) the number of clients and the cumulative percentage through that category. Each category is described as follows: A = 100% employed, B - 75% employed, C - 50% employed, D - 25% employed, E - 0% employed.

TABLE 4

PRETREATMENT RATE OF CRIMINAL ACTIVITY

CATEGORIES *	A	B	C	D	E
DRUG-FREE	1 - 13%	2 - 38%	2 - 63%	1 - 78%	2 - 100%
OTHERS	0 - 0%	2 - 6%	12 - 44%	9 - 72%	9 - 100%

* *Under each category (A, B, C, D, E), for each population is listed the number of clients in that category and the cumulative percentage of clients through that category. Categories are described as: A - no criminal activity, B - occasional misdemeanor, C - occasional felony, D - moderate amount criminal activity, E - heavy criminal activity.*

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THE NIDA CLINICAL STUDIES

A POINT OF VIEW CONCERNING TREATMENT APPROACHES WITH NARCOTIC ANTAGONISTS

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When narcotic antagonists were first introduced into the treatment of drug addiction, patients were placed on the medication without regard to selection criteria and assessments of "successes" or "failures" were made only on the basis of their retention in the program. Since that time, however, our evaluation criteria have become more refined and we have begun to look at more complex questions such as: Are these compounds "helpful" and if so, "for whom" and by what treatment techniques can we augment their usefulness? A salient aspect of our naltrexone studies, for example, is addressed to the question of "for whom?" Hopefully when our data analysis is completed, it will contribute to either affirming or negating the conceptual model that we have formulated to aid us in the differential diagnosis and treatment of opiate dependent individuals.

For my presentation today I have chosen to share with you some aspects of our point of view concerning treatment approaches based on our clinical experience. As investigators, we are all committed to the rigors of science with its demand for carefully controlled data. However, I am not addressing myself to specific research data, but rather to some issues concerning the application of this class of compounds to clinical treatment programs.

Although we are using psychoactive compounds sharing a specific pharmacologic property that can and has been used advantageously -- it would, in our opinion, constitute a serious error for a treatment program designated to evaluate their clinical efficacy to use the same model as that used to evaluate other pharmacologic therapies: compounds, for example, whose purported function is to alter an underlying physiologic malfunction or disease

process and which may relieve, eliminate or worsen a "target symptom." It is easy to discern drug effects when they cause a marked change (positive or negative) on some aspect of the psychopathology being examined -- such as the effect that lithium has on a manic reaction or imiprimine on depressed states. Narcotic antagonists do not directly affect an individual's psychopathology; their benefit is only secondary, by protecting the patient from the effects of self-administered opiates.

Therefore, the model to follow is not analogous to one in which you can explore the degree to which the compound, by itself, affects an identifiable clinical syndrome that, in most instances, is ego dystonic. Few people, for example, derive gratification from depressive symptoms. All addicts get gratification from their drug use, regardless of the consequent "secondary losses" that may be incurred. To pursue the analogy further -- we observe and describe varying degrees of "secondary gain" that patients may derive from their illness and that often lead them to interrupt their treatment regimen. The gain, however, for the individual addicted to drugs is "primary" not secondary. It is the "secondary losses" that bring him to us for treatment. We know with absolute certainty that antagonists prevent relapse to opiate addiction. It is contingent only upon the patient's continuing to take the medication at an adequate dose over a sufficient period of time.

Ah, there's the rub, --- PROVIDED HE TAKES THE MEDICATION. A major thrust of our clinical efforts, therefore, will need to be devoted to bringing to bear all our ingenuity and resourcefulness to help convert the ego functions of our patients so that their attitude toward continued opiate use is changed and it becomes viewed by them as a "primary loss" and not as a gain. In part, it becomes our ability to (and means wherein) we accomplish this task that must be evaluated. Thus the clinical efficacy of these particular compounds becomes inseparably bound to the efficacy of the clinics that use them.

I will discuss some of the clinical techniques we consider most important, although we must emphasize the obvious: Good clinical judgment is never fully explainable solely on the basis of specific techniques.

When working with narcotic antagonists, it is essential that the staff help patients to learn that their treatment is not the medication alone. Obviously, to do this, the staff themselves must know it, understand it and believe it! It takes a helluva lot more input to treat a drug addict than simply dispensing medication. As Dr. Lee Schwartz, a collaborator in our research, often reminds me: "It takes more than a pill to cure an ill."

The medication can, however, be used as a tool for the initial focus of therapy -- it can be a way of enabling the patient to begin to trust the therapist and to establish a therapeutic alliance. Whatever diverse therapeutic techniques are employed, we cannot overemphasize the importance of a good rapport and positive transference between the patient and a therapist. This relationship can be beneficial in many ways -- ranging from providing support the patient needs during the post-withdrawal period to substituting for emotional resources that are lacking in the patient's life. When we first began working with antagonists and did not provide such therapy, our results were poor; they improved when each patient was assigned to a trained and empathic therapist and was seen regularly, even if contacts were only brief.

Gradually, the patient can learn to look to the therapist -- rather than to opiates -- for gratification of dependency needs, relief of anxieties and solutions to the problems and dilemmas of his life. It is through this therapeutic relationship that a patient can get positive reinforcement for making choices that will contribute to his achieving a more stable, socially acceptable lifestyle, while deconditionins (or at-least non-reinforcement of his drug-seeking behavior is taking place.

One aspect of treatment that should be considered is the benefit a patient may derive from

having conditioning theory explained to him, so that he may begin to look for signs of conditioned responses within himself. The value for the patients who have this understanding has been remarkable in some of our follow-up interviews. When conditioning is explained to patients, it has the additional benefit of alerting them to the possibility that they could become readdicted at some time in the future -- even after a long period of successful antagonist treatment.

However, stopping the antagonist and resulting opiate use is, by itself, an insufficient criterion for labeling the treatment a failure. Would you say that digitalis is not clinically efficacious if a patient with congestive heart failure stops taking it? In our studies we have found that the length of time patients take naltrexone increases with each successive readmission.

The model we use should be similar to the one we use in treating chronic medical illnesses. A patient must be told that whenever medication is discontinued, he can and should ask to be put back on the antagonist whenever he feels tempted, or has begun, to use opiate drugs again. Imagine the positive affect it has on patients and their families when they can view addiction as no worse than other recurrent medical problems for which treatment is available. The emotional impact on the patient is usually profound, since he has previously experienced negative attitudes and rejection -- if only by being labeled a "failure" -- whenever he has become readdicted. When the treatment staff is nonjudgmental about his opiate use, it just "blows their minds." We've seen this happen over and over again -- "You mean, Doc, if I goof up, I really can come back to the program???"

The focus of treatment needs to become for patients to change their "lifestyles," rather than to "never use drugs again." If this is the correct focus, as we believe it should be, then it follows that the treatment staff must believe it, in order to convey it to the patients. For certain individuals, a meaningful commitment to rehabilitation with an antagonist can only be made after relapsing and becoming readdicted one or more times. For some it entails getting disgusted with themselves, others need to know their therapist long enough to trust that the therapist cares about him and his needs and will reach out to help him through times of stress.

We have found that the most successfully rehabilitated patients are those who learn to rely more and more on the therapist for help, especially during the early phase of treatment. As this relationship begins to become a trusted and consistent source of satisfaction, these patients dwell less and less on the instant gratification afforded by opiates.

Here, a specific case example may best illustrate this point:

A 28-year-old man who had been on methadone maintenance in our program for four years, felt "ready" to be drug free, having made significant changes in his life while on methadone. His therapist concurred, but suggested naltrexone as a transitional treatment. He initially refused, stating that he felt he didn't need it. For two months following the last methadone dose, he struggled against growing temptation to use opiates to relieve his secondary abstinence symptoms and severe depression, which seemed to get worse instead of better as time went by. He had 400 mg methadone at home and became obsessed by the thought of the instant relief it would offer. During this period he saw his therapist daily and called her frequently at night or on weekends, when he was under stress or having severe symptoms. Finally his symptoms became so severe he knew he could no longer resist the temptation to use dope again without more help. He phoned the clinic and was told to come right in, which he did. Riding through East Harlem -- where he used to take drugs -- on his way to the clinic he experienced severe withdrawal (conditioned abstinence) and was tempted to get out and cop some dope. He arrived at the clinic and said he felt it was necessary to try the original suggestion that he take naltrexone.

On follow-up, he stated that he knew the naltrexone would give him "peace

of mind," since he would be protected against losing control and impulsively using drugs. He added, however, that without the on-going relationship with his therapist, he would have given in to his urge to use dope and if he did so even once, he would have become readdicted, felt himself to have failed, and perhaps never tried to detoxify again. He said his experience led him to feel that in the initial opiate-free months, it was his therapist that helped first, then it was the naltrexone, but without both of these factors. he couldn't have achieved his goal. He took naltrexone for one month only, then stopped when he felt ready. Today, more than two years later, this patient continues to be opiate free. We have had many patients express the same theme: The antagonist and the therapist must work together to help them.

Clinic attendance is also a crucial issue. Methadone patients come because they fear getting sick: antagonist patients don't have that worry. Their attendance must be based on a strong desire to remain drug-free, fear of family or other external pressure, or a good relationship with their therapist. Few patients can be expected to come to the clinic because of a commitment to their therapist initially. It becomes a very strong message to the patient, however, if he skips one day of medication and is called by his therapist to find out where he is. Our patients often express surprise and state that they have never been "cared about in this way" by other treatment programs. A few such calls, and soon many patients begin to respond to that caring with a commitment to their therapist that includes coming to pick up their medication.

Requiring daily medication is usually a good idea with antagonist patients, at least in the initial months of treatment. It not only provides some structure to their lives and puts them in frequent contact with the staff, but also can serve to alert the staff to the potential for readdiction whenever a patient skips a day of medication. Many patients feel they can skip medication and use opiates "once in a while." We have found that antagonists become useful in respect to this issue for two reasons. Since the patient must make a conscious decision to skip medication, he cannot deny responsibility for his impulsive drug use. Many good antagonist candidates -- those who we believe have the best prognosis -- are also those whose drug use is impulsive.

By helping the patient understand these dynamics, the therapist forces the patient to become aware of his choices, instead of believing that he used drugs because he was-"weak-minded" and implying it was beyond his control. We often tell patients and their families that refusal to take medication is analogous to stating an intention to get "high." A patient who is ambivalent about taking medication on a particular day is less likely to act on his impulse to skip it, if he knows that doing so is equivalent to announcing to his family and the staff: "Today I plan to shoot heroin." We have found that involving the family in this way places the patient in a situation where he can rely on external pressures to help him through times of ambivalence, until he can integrate his desire to remain drug free on a new emotional level, under more conscious control.

In conclusion we strongly urge that you treat your study subjects as patients -- exercising the same degree of concern, interest, sincerity and dedication to relieve human suffering and to restore health as you would do for any other sick person.

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CLINICAL EXPERIENCES WITH NALTREXONE IN 370 DETOXIFIED ADDICTS

Muriel Thomas, R.N., Frank Kauders, M.D., Marcel Harris, Judy Cooperstein, R.N., Gordon Hough, Ph.D., Richard Resnick M.D.

INTRODUCTION & BACKGROUND

The Division of Drug Abuse Research and Treatment of New York Medical College began to use naltrexone in 1973. Since then, 370 opiate addicts have been detoxified and inducted onto naltrexone. The Division's clinic is located in East Harlem, where there is a high incidence of opiate addiction. Thirty-eiaht percent of the patients treated at the Division are black, 38% are Puerto Rican, and 24% are white. Heroin and/or illicit methadone are the drugs primarily abused. Patients being treated in the Division come from all levels of society though they are predominantly a low socio-economic group. They are referred for treatment from community agencies such as probation and parole officers, from nearby ambulatory detoxification facilities, and by patients who have told their friends and relatives about naltrexone.

When our investigations of naltrexone first began, many patients seeking treatment were suspicious of a new medication. Cyclazocine was fairly well-known in the community. Although it was disliked at some treatment facilities, patients at New York Medical College had been inducted and maintained on it without undue difficulty with side effects. When we began using naltrexone it was necessary to do public relations work so that both staff and patients would be willing to explore how satisfactory naltrexone would be as treatment.

SAFETY & SIDE EFFECTS

The first and probably most important finding from treating these patients with naltrexone is that

naltrexone appears to be a safe drug with very few side effects. The side effects which appear most frequently (though in a very small number of patients) are epigastric pain, especially if the medication is taken on an empty stomach, and clinically insignificant elevation of blood pressure. Epigastric pain began to occur less frequently when induction procedures were changed. In the earliest patients, this was the only symptom on the check list that increased when naltrexone was given following seven opiate free days and a period on placebo. Such pain usually made patients reluctant to take a second dose.

Narcan injections (0.8 - 1.2 mgs naloxone i.v.) were introduced prior to administering naltrexone. If the injection precipitated any symptoms of withdrawal, the start of naltrexone was postponed until the Narcan test was negative. For most patients, the Narcan test has allowed induction on a 100 mg dose of naltrexone with no discomfort. This finding suggests that for many patients this pain was secondary to precipitated abstinence. A very small number of patients still experience epigastric pain. These patients often have a history of gastrointestinal complaints previous to their seeking treatment. The pain they experience when they take naltrexone can usually be controlled with an antacid or by having the patient eat before ingesting the medication.

TREATMENT CONSIDERATIONS

Our second finding is that naltrexone has been extremely valuable to many patients, although to be most effective it requires a positive staff attitude and a multimodality treatment program. Methadone maintenance should be available for those patients for whom antagonist treatment seems unacceptable at a particular time. Records of the flow in and out of treatment of 262 patients during the past year and a half indicate that about 40 have returned for readmission up to three times. At this writing (May, 1976), 9 of the 50 patients currently receiving naltrexone had dropped out of treatment, become readdicted, and then returned. Our data show that patients remain in treatment longer with each successive readmission.

During the past 18 months, 20 individuals took only one dose of naltrexone, 39 took naltrexone more than once but for less than one week, 132 for between one week and three months, 50 for between 3 and 6 months, and 21 for more than 6 months.

A search for factors that predict response to naltrexone at intake has found very little, beyond patients' stated wish to become drug free. We believe that individual counseling that begins with a sensitive and careful intake interview and history is an essential part of naltrexone treatment. The degree to which a counselor can involve the patient affects retention and return to treatment more, for example, than apparent motivation at intake or psychosocial status. During counseling sessions our staff helps patients talk about and clarify ambivalent feelings about being drug free. Staff emphasize that medication alone is not a cure for patient's desire to use drugs. Our experience has led to the view that treatment is a process frequently involving periods of progress followed by periods of relapse. We communicate to the patient that he should return to treatment if he is tempted to use or becomes readdicted. One of the special virtues of naltrexone is that patients may resume taking it when opiate use tempts them. They need not fear that they will later have prohlems stopping naltrexone.

Some patients may develop transference to the institution rather than to an individual therapist. Most often such patients have difficulty with closeness and are socially isolated. One patient came to our clinic five days a week for many years. He refused a three day a week schedule when he was on methadone. When he detoxified and was inducted onto naltrexone he continued to come to the clinic five days a week. Recently he has accepted a three day a week schedule. He has only a superficial relationship with staff members, although several have tried to engage him in treatment. His transference is with the nurses and

the clinic in general. He must continue to come to the clinic three days a week to continue to receive naltrexone, but our staff has the impression that in the absence of close relationships he takes naltrexone in order to come to the clinic, as well as vice versa.

In general our staff accepts treatment that goes forward in these ways. Patients enter, leave, and return to treatment. They find rewards in the staff and clinic, rather than simply in the medication. In our clinic we are not surprised that patients who are accustomed to immediate gratification find it hard at first to stay in treatment, but return to us later. Very few patients can learn to manage a disorder as complicated as opiate addiction during their first involvement in treatment. Most often time is needed to work out ambivalence about treatment and about change.

SPECIAL INDICATIONS FOR NALTREXONE

We have found that naltrexone is useful for certain other specific groups in addition to street addicts. The first are detoxified methadone patients. We are studying naltrexone as a transitional treatment for these patients following their detoxification from methadone. In a double blind trial comparing naltrexone and placebo, 25 patients have been treated. Patients chosen for this trial have been on methadone for periods between 1½ and 3 years, work or go to school and have not abused opiates for six months or longer prior to beginning detoxification. After obtaining an informed consent, patients were randomly assigned to either active or placebo naltrexone. The first 19 patients were evaluated by staff for subjective effects and participated in therapy with their counselors. The most recent six patients were assigned to one observer blind to their medication to control for differences in both subjective effects ratings and counseling. All patients were told that the medication might help relieve the discomfort that usually occurs following methadone detoxification. The antagonist properties of naltrexone were minimized.

All patients receiving active naltrexone showed a tendency toward less severe symptoms compared to those receiving placebo. The differences between groups were not statistically significant. The most recent 6 patients were also compared for response during clinical interview. Some patients focussed on difficulties they were having in interpersonal relationships at home, work or school. Less frequently somatic complaints were discussed. For other patients the reverse was true: during clinical interviews they focussed on their somatic complaints more than on interpersonal problems. When the double-blind code was broken 6 months after detoxification or at termination of treatment, the patients who focussed on interpersonal problems were found to be on active naltrexone. Patients primarily concerned with somatic complaints were found to be on placebo. In one remarkable case, a patient who focussed on difficulties in his relationship with his girlfriend during the first eight weeks of treatment began to complain in the ninth week about severe somatic symptoms including joint pain, stomach cramps, and excessive tearing and sweating. The observer recorded this change in the patients chart. When the code was broken, we learned that the patient's medication had been changed from active to placebo for unrelated medical reasons at the same time as the observer had seen the clinical change in the patient's concerns.

The differences between these groups suggest that naltrexone may alleviate secondary abstinence symptoms, especially lethargy, weakness, poor appetite, and poor concentration. Patients who felt that naltrexone was helpful had received active medication, while those who reported little if any relief had received placebo. These trials are continuing. Continued findings of clear differences between active and placebo naltrexone would be an important contribution to treatment, in light of the difficulty which many patients report, and which is clinically observable, in detoxifying from

methadone maintenance. Naltrexone maintenance for several months after methadone detoxification can also prevent impulsive use of opiates and readdiction during this high risk period. Proposals for future use of naltrexone should not overlook this potential area of investigation.

The second type of opiate dependent individual for whom naltrexone may be the treatment of choice is the opiate-abusing medical professional. Several physicians who were addicted to meperidine (Demerol) or pentazocine (Talwin) have been treated in our clinic with naltrexone. For these patients, arrangements were made with another physician who supervised their ingestion of medication in lieu of their coming to the clinic. Approval for these arrangements was granted by the FDA. We do not know of any other more appropriate treatment for these individuals who are professionally competent but were unable to sustain opiate abstinence. All received concurrent private psychiatric treatment.

FUTURE DIRECTIONS

It is now possible to present clinical impressions of the differences between cyclazocine and naltrexone in treatment. Induction onto naltrexone is much easier, quicker, and freer from side effects than induction onto cyclazocine. Cyclazocine patients were always hospitalized during induction, induction took longer, and patients usually remained in the hospital until all side effects had subsided. During this time a therapeutic relationship could be established. Patients taking naltrexone, however, usually leave after the first dose; there is no therapeutic reason for them to stay. Too often, patients drop out of naltrexone treatment before they have established therapeutic ties with the clinic. In addition, naltrexone is also far easier to discontinue than cyclazocine. Abruptly stopping cyclazocine causes withdrawal symptoms that serve as a reminder to take the medication. That reminder made it more difficult for patients to miss clinic visits impulsively. These differences in ease of induction and termination suggest possibilities for the study of a combined naltrexone-cyclazocine therapy in which patients are first inducted on naltrexone and then begin to receive cyclazocine concurrently. After maintenance dose of cyclazocine is reached, naltrexone could be withdrawn and the patient maintained on cyclazocine. We are planning a systematic assessment of this combination.

The development of long-acting antagonist preparations would make it more difficult for patients to resume using opiates when they cannot or will not come to the clinic. Evaluation of individual patient's treatment goals would be critical in their clinical application. An addict who does not desire treatment for social and psychological problems would not be appropriate since a long-acting preparation would enable him simply to stay away from the clinic and avoid the treatment he needs. Similarly a patient who abused other drugs whenever he was opiate free in the streets would seem like a poor prospect, at least until he had been in treatment long enough for staff to believe that his behavior had changed. On the other hand a patient whose life is stable but who still feels threatened by the chance that he will resume opiate use might receive an implant and return to the clinic every month or six weeks for the implant to be replenished or restored. In general it would seem desirable to evaluate patients on the basis of whether they still need or desire naltrexone but wish to stop taking it primarily because of the burden of frequent clinic visits. For this group of patients, the advantages of long-acting preparations would be enormous.

SUMMARY

Our studies have shown no evidence of toxicity and few side effects from naltrexone. It is a valuable adjunct in treating addicts who wish to be opiate free. Patients who drop out and return to treatment tend to remain longer with each successive readmission. Naltrexone has special potential for persons, such as an opiate-abusing physician for whom methadone maintenance is clearly inappropriate. A double-blind study has

suggested that it may have value as a transitional treatment for detoxified methadone maintenance patients. Differences between naltrexone and cyclazocine suggest that a treatment combining these drugs should be explored.

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NARCOTIC ANTAGONIST TREATMENT OF THE CRIMINAL JUSTICE PATIENT- INSTITUTIONAL vs OUTPATIENT- INCLUDING A 24 HOUR DETOX NALTREXONE INDUCTION REGIMEN WITH ORAL MEDICATION

Leonard Brahen, Ph.D., M.D., Victoria Wiechert, MPS, Thomas Capone, Ph.D.

INTRODUCTION

A uniquely compatible affiliation exists between the concepts of the criminal justice and correctional systems and the treatment of opiate addiction through the Department of Drug and Alcohol Addiction in Nassau county. The concepts of diversion and rehabilitation through the prevention of crime by the elimination of causes are merged with medical treatment as co-existing, independent components under one comprehensive process. The Nassau County Department of Drug and Alcohol Addiction administers joint antagonist programs under this process; The Narcotic Antagonist Work-Release Program and the Antagonist Treatment Clinic. Institutional vs outpatient, respectively.

NARCOTIC ANTAGONIST JAIL WORK-RELEASE

PROGRAM

In late 1972, the Nassau County Department of Drug and Alcohol Addiction and the Nassau County Correctional Center in a joint undertaking initiated a Narcotic Antagonist Jail Work-Release Program. This program is now located in the Work-Release Facility, the minimum security area of the Correctional Center complex. It is specifically designed to incorporate the addicted inmates into the regular Work-Release Program by using fully protective doses of a narcotic antagonist, thereby immunizing addicted inmates against a narcotic high,

I. TYPES OF PATIENTS TREATED

Patients are inmates from a maximum security correctional center who have requested privilege of work-release.

In this program the inmate candidate writes

a letter requesting work-release to the Work-Release Director. The inmate's record and history are evaluated and he is given an interview. He then is presented to the Nassau County Correctional Center Board for approval for the Work-Release Program.

Most of the inmates serviced were under twenty-three years of age and approximately evenly divided between Caucasian and negro. Almost half had never been married and over one-third were divorced or separated. Approximately one-half never completed high school and fully one-third had not been employed on a full time basis in the six months preceeding admission to the jail. One-fifth had been supported by public assistance before admission. Most of the inmates had a history of four or more arrests and convictions.

A. Criteria for Admission

The Nassau County Correctional Center Board selects suitable inmates having a prior history of narcotic addiction. Such voluntary applicants must meet all the criteria established by the Nassau County Work-Release Program. It should be noted that some New York State facilities permit release to parole earlier than usual, permitting the parolee to go on work-release in his respective county facility, thereby affording him an opportunity to continue employment on release. This should substantially increase the patient population pool of work-release candidates.
Essentially healthy volunteer subjects are inducted onto the naltrexone program. They must fulfill the following criteria:

1. Age: 18 - 45 years old

2. Sex: Male

3. Selection: All adult male inmate subjects passed by the Correctional Center Work-Release Board and accepted for this study should beinreasonably good-physical and mental health with a documented history of narcotic addiction All subjects will have been detoxified and completely free of narcotics for a minimum of seven days prior to antagonist administration.

B. Admission Procedure

1. A complete history is obtained, physical examination given and laboratory tests performed before the inmate enters the program as follows:
(The starred examinations and laboratory tests are done monthly)

*a. Physical examination
*b. Neurological examination
c. Chest X-ray
d. Slit-lamp eye examination
*e. E.K.G.
*f. Urinalysis
g. Prothrombin time
*h CBC (with differential)
*i. SMA -- 12/60 and 6/60
j. Australian Antigen
k. VDRL
*l. Reticulocyte
*m. Platelet count
n. Sickle Cell

2 .Psychiatric Evaluation and Psychological Testing for baseline data and treatment planning is conducted on entering the program, and repeated at appropriate time intervals. The Rorschach, MMPI, Locus of Control as well as a Psycho-Social History are administered routinely upon admission.

3. Each subject voluntarily agrees to enter this drug treatment program after it has been fully explained to him, (including sufficient information about the possible harmful effects of the investigational antagonist so that he can make and sign 1) an informed consent, and 2) a Rules and Regulation contract, signed prior to his participation in the program. At the time of the interview for work-release the informational brochure is reviewed with the candidate inmate.

C. Patient Care Procedures

1. Naltrexone Induction

Opiate addicted inmates are detoxified in the maximum security facility upon entry and are therefore "clean" for at least a month before entering the Work-Release Program. All of our entering patients are housed in minimum security modules where in the first few weeks they are not permitted out to work so that the controlled induction studies can be accomplished. These studies are designed to compare three different acute dose levels and different dose regimens and ultimately withdrawal studies, all with well controlled double-blind protocol.

2. Daily Medical Administration

a. Naltrexone or placebo are administered orally each morning before work and each evening after work, according to the plan outlined in the present double-blind (3-D) protocol.

b. Urines are monitored by daily evening collections and analysis for commonly abused drugs. Breathalyzer tests are done when warranted.

c. Vital signs are monitored b.i.d., morning and evening (e.g. blood pressure, pulse, respiration and temperature) and weight is noted every week.

d. Behavioral and somatic symtomatology is re-

corded twice daily by the nurses and by the inmates on the double-blind report forms in mini-counseling sessions.

All induction medication active and placebo is like-looking-and-tasting liquid in a cherry syrup base administered at 6 A.M. and 7 P.M. daily. The medication is coded by subject number, day of treatment and whether A.M. or P.M. dose. It is premeasured for dispensing to the patient in 2% oz. plastic disposable wide mouth bottles with a screw top. The volume is brought up to 20cc with the addition of a dark colored cherry syrup to standardize color, taste and volume for the double-blind studies. At the time of administration to the patient apple juice or orange juice is added.

3. Non-Pharmacological Support

a. Group and Individual Counseling: Patients in the Work-Release Program are seen one evening a week in group therapy sessions and one evening a week in individual sessions as needed. These sessions are conducted by appropriate licensed professional workers (e.g. physicians, psychiatrists, psychologists, social workers, nurses) ,

b. Vocational and Educational Services: Vocational interest inventories, preference schedules, and special aptitude tests are administered. The qualified inmate may receive financial support for vocational training through the New York Office of Vocational Rehabilitation. Such support may be continued upon release from work-release. Continued financial support requires a minimal level of performance. Educational assistance and guidance are provided for those who have terminated their education prematurely and wish to resume their studies.

c. Community Adjustment: A Social Worker from the Nassau County Department of Drug and Alcohol Addiction, Social Service Department aids the inmate's re-entry into society including adjustments required in planning work, family, economics, legal problems, treatment programs, etc. Supportive community services are provided and appropriate referrals and contacts are made.

A Community Relations Coordinator is assigned the responsibility for continuing contacts and obtaining follow-up data.

ANTAGONIST TREATMENT CLINIC

The Antagonist Treatment Clinic is an out-patient facility located on the grounds of the Nassau County Medical Center complex. It was initially started to continue the post-incarceration patient following his release from the Work-Release Program. It has expanded to include Parole and Probation patients as well as other agency referrals and "street talk" referrals,

It is a logical extension of the Narcotic Antagonist Work-Release Program, its objective is the interception of a law offender with a narcotic addiction history, enroute to incarceration. The interception should avoid the high cost recidivism cycle. This program will provide an alternative to the drug-free treatment programs and methadone programs now available to probation and parole.

I. Type of Patients Treated

These are out-patients who have the legal restrictions mandated by probation or parole, other agency referrals, and "street" referrals.

Demographic information on these patients is similar to the work-release population.

The candidates for this program are accepted after an interview with the Director or Deputy Directors and consulation with staff members.

Essentially healthy volunteer subjects are permitted entry into the Antagonist Treatment Program.

A. Criteria for acceptance are as follows:

1. History of opiate addiction, documented or certified, no time limit.

2. Age: 18-45 years old.

3. Sex: Primarily males. Female candidates require special consideration of risks over benefits. Pregnancy during antagonist treatment is contra-indicated. Therefore, preventive measures such as an IUD or the "pill" are mandatory. Special approval from F.D.A. must also be obtained.

4. Health Status - All subjects must, after examination, be in reasonably good physical and mental health.

5. Motivational Status - Should be at such a level as to give some assurance that program requirements will be adhered to.

6. When the court requires a probationer or parolee be protected from addiction by chemical means, the antagonist can serve as a methadone alternative having a non-addictive relatively

safe profile with no street value.

7. Detox - The candidate must be detoxed for at least two to four days. In some selected candidates a transition detox antagonist induction can be done in one day (described in Part IV).

B. Admission Procedure

The admission procedure for out-patient treatment is followed as outlined under the Narcotic Antagonist Jail Work-Release Program.

C. Patient Care Procedures

1. Opiate Detoxification and Naltrexone Induction.

In preparation for naltrexone induction the patient is detoxified from opiates in one of three ways:

a. Hospitalized for ten days in a Psychiatric Facility and detoxified using methadone with daily reduction of dosage and controlled withdrawal.

b. Self-detoxification - "cold turkey" out-patient.

c. Transitional one day detoxification - naltrexone induction procedure whereby detoxification and naltrexone induction are accomplished in twelve to twenty-four hours (described in Part IV).

In general all patients on the day of induction receive naltrexone as follows: 5 mgm initially, followed by 10 mgm, 10 mgm and 25 mgm with 20 - 30 minute intervals in between doses.

2. Medical Administration

a. Patients are maintained on 50 mg naltrexone daily for two weeks, then given three days a week with 100 mgm on Mondays and Wednesdays and 150 mgm on Fridays.

b. A urine is collected at each visit and sent for analysis of commonly abused drugs.

c. Vital signs are monitored at each visit and the patient weighed every week.

d. Behavioral and somatic symtomatology is recorded at each visit in mini counseling sessions.

3. Non-Pharmacological Support

a. Group and individual counseling: Patients are seen one evening a week in group therapy and by appointment for individual counseling.

b. Vocational and educational services: Various vocational tests are administered as the need arises. Educational assistance and financial support for vocational training through the New York State Office of Vocational Rehabilitation are available.

c. Community adjustment: The Social Service Department of the Nassau County Department of Drug and Alcohol Addiction provides counseling, referrals and contacts for adjustment toward work, family, community, etc.

A Community Relations Coordinator is assigned the responsibility for community contacts and follow-up data.

II. PRACTICAL EXPERIENCE WITH NALTREXONE TREATMENT

A. Our experience suggests that the three times a week dosage regimen is feasible and practical for both the institutionalized work-release and out-patient populations in a strictly treatment oriented setting for highly motivated persons. However, with this regimen, some therapeutic intimacy is lost so that opportunity for effecting behavioral change is lessened. This is one reason twice daily contact through the controlled double-blind study is still maintained in the Work-Release Facility.

In an attempt towards greater motivation for program participation, antagonist treatment is presented as a high status program for select, treatable persons.

Preparation of our incarcerated population for re-entry into the community is an important facet of our treatment package. This is evidenced by the fact that approximately 23% of Work-Release Program patients are taken off the program and sent to maximum security for work-release infractions. Aggressiveness and negativistic behavior emerge as the release date grows nearer, usually from several days to a month before release. Patients often express a fear of freedom in the community and going back to family situations. Retention of patients in the controlled incarcerated seting is approximately 70-75%.

Retention of patients in the out-patient clinic is much less, ranging from 4 days to 590 days for the first treatment phase with a mean of 62.3 days (N=33, S.D. 114.9). Those who entered the second treatment phase stayed in treatment ranging from 1 day to 91 days with a mean of 2097 days (N=14, S.D. 25.81. Even with the imposition of rules and regulations and the conditions of probation or parole there is sporadic absence from

treatment. In an effort to maintain continuity of care and responsibility, patients are permitted treatment re-entry.

The Work-Release patients as a group demonstrate a great deal of group cohesiveness. If there is a strong, aggressive, dissatisfied leader, the group becomes quarrelsome with the staff and officers and demonstrates dissatisfaction and somatic concerns. In another time span, with other patients, group members are cooperative and have few complaints.

In contrast the clinic patients as a group are not united. They are impatient, restless, and have a short attention span. Detachment and finally group disintegration often takes place. This was a consistent pattern with several groups that were started out-patient.

We have treated four female outpatients Due to community minority group pressures, the Correctional Center authorities have requested that we treat females on work-release.

B. Uses of Naltrexone

Naltrexone supplemented by supportive services is a valuable rehabilitation tool in a correctional setting with rules and regulations set and implemented by correctional staff. It is also a valuable diversion technique whereby the legal restrictions of probation and parole operate to interrupt the cycle of repeated incarceration.

Methadone at this time is the primary drug treatment for narcotic addiction. The use of methadone has produced problems owing to the drug itself, such as: 1) creating a "legal" addict including the adolescent heroin user with a questionable addiction history; 2) deaths attributed to legal methadone obtained through illicit channels; 3) promotion of criminality owing to its high "street" value.

There is a question as to whether it is ethically appropriate for the medical community to provide a highly addictive substance on a continuing basis to the heroin addict and the alleged heroin addict as well as to the usefulness of treatment with high doses of narcotics which virtually bind the patient to a lifetime in this addictive state.

Naltrexone, which is a non-addictive, relatively safe agent with no "street" value provides an alternative treatment modality to methadone and drug-free programs, especially where strong motivation for self rehabilitation is present.

As a transitional modality, naltrexone may be used as an antagonist bridge from methadone to a drug-free state by Phase III and IV methadone patients who have not been able to reach the drug-free state alone or wish to discontinue methadone maintenance.

When working with out-patients, the detoxification from opiates often presented a problem. Our general detox procedure which required expensive and prolonged hospitalization was difficult for many patients who had jobs, family responsibility, etc. For these patients a one day transition detox-antagonist induction was designed, whereby valium and compazine are administered initially, at 4 hours, then at various awareness levels, before the anticipated symptomatology of withdrawal begins. This regimen minimizes gastro-intestinal symptoms and the severity of somatic and muscular spasm, and eases the anticipated tensions of withdrawal. Naltrexone induction is started at a very low dose. This precipitates withdrawal, but with a lower level of discomfort than usual. Valium and compazine are administered periodically to maintain the initial sedation and anti-emetic and anti-nauseant level as naltrexone dosage is periodically increased until full blockade is reached (50 mgm). This process usually takes from twelve to eighteen hours with frequent monitoring of vital signs and accurate recording of symptoms, complaints and procedures by the nurse in attendance.

There are several advantages to this method of detoxification: 1) Only one or two days at most are lost from the patient's regular activities as compared to the lengthy institutional detoxification. 2) The discomfort of withdrawal is minimized compared to the severity of self, drugless detox. 3) There is a great monetary saving. The cost of a one day detox is minimal compared to the expensive institutional detox of approximately $1200-$1400.
When rapid oviate detoxification is desired. the transitional detox-naltrexone induction' method, as described, is an alternative for the traditional methods.

III SAFETY OF NALTPEXONE

It appears, from our studies, that naltrexone is a relatively safe antagonist. A full blocking dose can be administered to the opiate-free patient without incremental induction doses, and without producing any untoward effects. Naltrexone maintenance doses can be abruptly withdrawn without any withdrawal effects. (Brahen, Capone, Wiechert, Desiderio, 1976).

In general our follow-up laboratory and other examinations showed significant changes in some areas, from pre-drug baseline examinations, but all still within normal limits. (Brahen, Capone, Wiechert, Babinski, Desiderio, 1976).

The following tests were significantly altered when pre-drug and post-drug data (100-200 days) were compared.

Naltrexone induced a significant depression in the following (but, both pre and post drug data are within normal limits): BUN. platelets, cholesterol, systolic and diastolic mean blood pressure. An increase was noted for uric acid and prothrombin time. In no instance was either pre or post-drug data outside normal limits. Such changes as noted are merely suggestions and should be followed up.

For neutrophils, lymphocytes and SGOT the mean pre-drug values were abnormal and remained abnormal in the post-drug period, but did not change significantly as a result of drug administration.

No significant changes were revealed when pre-drug EKGs were compared with repeat EKGs. (Brahen, Capone, Wiechert , Babinski , 1975) .

IV. FUTURE STUDY AND USE OF NALTREXONE

The evidence we have collected indicates orally administered naltrexone to be a relatively safe, low symptom producing antagonist even at high doses.

Not all somatic and behavioral symptoms can be attributed to drug effect. Certain individuals who can be identified with psychological examinations show a greater tendency to experiencing ontoward placebo and drug effects. (Brahen, Capone, Wiechert, Desiderio, 1976). The importance of supportive services cannot be over emphasized.

Presently and in the near future, orally administered naltrexone will be used as a transitional modality from an opiate, such as methadone, to a drug-free state. Beyond this, with the emergence of long-acting naltrexone for long term immunization, this antagonist may well be the drug of choice in the control of opiate addiction. (Reuning, et. al.).

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USE OF NARCOTIC ANTAGONISTS (NALTREXONE) IN AN ADDICTION TREATMENT PROGRAM

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The Washingtonian Center for Addictions in Boston, Massachusetts has offered opioid-addicted patients the option of receiving a long acting narcotic antagonist, naltrexone, in conjunction with their regular course of treatment, since January 1, 1974. The primary objectives of this program are: 1) to evaluate the physical and behavioral effects of naltrexone; 2) to assess the safety of naltrexone; and 3) to investigate the clinical efficacy and usefulness of naltrexone in an ongoing treatment program for addicts.

Between January 1, 1974 and May 1, 1976, twenty patients received naltrexone for varying periods of time. This paper will report findings on the initial naltrexone treatment experience in this group of patients.

PATIENT SELECTION

During this study period 703 male patients between the ages of 18 and 47, hospitalized at the Washingtonian Center for Addictions for opioid detoxification, were informed about naltrexone treatment in small groups which focused on post-hospitalization treatment alternatives. Any individual patient expressing interest in exploring the usefulness of narcotic antagonists in his rehabilitation was scheduled to discuss his interest with the Coordinator of Outpatient Drug Programs. During this meeting an evaluation of the personal, social-psychological and drug history was carried out, followed by a discussion of treatment alternatives. Naltrexone was presented as one of several options. If patients selected naltrexone, they were told that

treatment would involve daily attendance at a clinic and appropriate counseling no less frequently than once a week. In addition, participation in a safety and efficacy study was required because of the investigational nature of the drug. After a detailed explanation of the experimental nature of naltrexone treatment, patients were given an informed consent to read. Patients then met with the Principal Investigator to discuss any questions and to sign the informed consent. This was followed by an additional discussion with the patient and signing of the informed consent by the hospital's Human Subjects Officer, who verified the subject's voluntary participation and checked on the subject's understanding of the risks involved in taking an investigational drug.

Of the 703 male patients undergoing opioid detoxification who were informed about the option of narcotic antagonist treatment, 131 expressed serious interest in the program. Forty-five (45) eventually signed informed consents, but only twenty subjects actually completed the baseline evaluation phase and received naltrexone.

PATIENT ATTITUDES TOWARD NALTREXONE TREATMENT

During the early phase of the study 'an evaluation was made of the attitudes and reactions toward naltrexone of male patients undergoing opioid detoxification.

Twenty (20) such patients eligible for the naltrexone study were interviewed with a structured questionnaire about their perceptions and expectations regarding naltrexone as a possible treatment for their addiction. Four of these patients later participated in the naltrexone study. All four felt, prior to receipt of naltrexone, that naltrexone would give them the time necessary to stabilize their lives.

Of the twenty patients interviewed half stated that they would not choose to receive naltrexone, for one of three reasons: 1) aversion to use of any chemical support; 2) dislike of program structure (daily clinic visits and many laboratory tests); and 3) general aversion to participating and "being used" in a new and unknown treatment method.

Ambivalence about the use of "another drug" was the most commonly reported reason for nonparticipation in a naltrexone program. There was almost a unanimous feeling on the part of these patients that they would not participate in methadone maintenance treatment and, even though they distinguish between the use of naltrexone in comparison to methadone, there was a generalized attitude that dependence on taking any drug was bad.

It was our expectation that patients would be concerned with the possible toxic and side effects of naltrexone and that this would be one reason for avoidance of the study. However, contrary to expectations, while patients were aware of the potential risk of toxicity and of side effects, only two of the 20 patients stated that such a risk would be a deterrant to participation in the study.

Later, patients undergoing opioid detoxification expressed another concern which emerged as a major reason for nonparticipation in the study--the fear of being unable to get high. This fear was often manifested by an intense concern about the details of naltrexone action. Specifically, patients would ask how long the effects of the drug last, what medications could be used for the relief of pain in case of an accident, and whether taking naltrexone for a period of time would alter their previously experienced reactions to opioids; that is, reduce their future ability to get high. In spite of reassurance that the project was entirely voluntary, that they could withdraw from the project at any time, and that they could still experience the opioid high after 24-48 hours after stopping naltrexone, several patients with this concern decided not to participate in the study.

DEMOGRAPHIC CHARACTERISTICS OF NALTREXONE PATIENT

Table 1 shows the demographic characteristics of the twenty subjects.

The mean age at the start of treatment was 27.8 years. The duration of addictive opioid use was 7.1 years with 20.8

TABLE 1

Table 1. Demographic Data - Naltrexone Study (n = 20)

	Mean
Age	27.8 years
Length of Addiction	7.1 years
Age of Initial Addiction	20.8 years
Previous Number of Treatments	4.1
Education	11.8 years
I.Q.	103.8
Race	**Percent**
White	85%
Black	15%
Religion	
Catholic	65%
Protestant	20%
Other	15%
Marital Status	
Single	40%
Married	35%
Separated/Divorced	25%

years being the average age at onset of addiction. The average oatient completed high school and was in the normal range of intelligence. The mean number of previous treatment attempts was 4.1 and included psychotherapy, detoxification, methadone maintenance, and therapeutic communities. Fifteen (15) percent of the patients were employed at the time of naltrexone induction.

The patients who volunteered for naltrexone were demographically more like the patients on our methadone maintenance treatment program than the patients on our detoxification program, even though those who volunteered for naltrexone actually were on the detoxification program at the time they volunteered. Naltrexone patients are older than patients on the detoxification program, more are white, and more are working at the onset of treatment.

STUDY PROCEDURES: NALTREXONE INDUCTION, PHYSICAL AND BEHAVIORAL MEASURES

Most of the patients were hospitalized throughout the detoxification period. During this phase, they had neither visitors nor passes. They participated in daily group psychotherapy along with other (non-naltrexone) drug patients who were being detoxified. After detoxification was completed, baseline measures of physical status, including Sympton Check List, chest x-ray, ECG, and blood tests, were performed. Several baseline psychological tests were also obtained: Current and Past Psychopathology Scale (CAPPS); Wechsler Adult Intelligence Scale (WAIS); the Minnesota Multiphasic Personality Inventory (MMPI); and Profile of Mood States (POMS). Subjects also received naltrexone placebo daily during this baseline period. During the baseline period, seven to ten days after the last detoxification dose of methadone, naloxone challenges were performed. During the challenge the physicians, nurse, and counselor were present and pupillometry, pulse, blood pressure, and observations for signs of withdrawal were recorded. Following the naloxone challenge, naltrexone was substituted for placebo in increasing 10 mg doses until a level of 50 mg was reached. At this point, most patients were attending our outpatient clinic and received the 50 mg maintenance naltrexone dose daily. Some patients chose to enter half-way houses or stay at the Extended Inpatient Service of the Washingtonian Center for Addictions, an eight-week rehabilitation program focusing on prevocational adjustment skills. All patients were required to participate in individual or group psychotherapy and to participate in repeated measures to assess the safety of the drug. In addition to these measures, the Symptom Check List and Profile of Mood States (POMS) were administered bi-weekly. The Symptom Check List is a list of 37 physical and psychological states or experiences. All patients were asked to rate themselves on the basis of absence or presence of the symptoms within the preceeding 24 hour period. A score of "0" indicates "not at

all"; 1 indicates "mild"; and 2 indicates "severe". The POMS is a self-rated questionnaire with six factors; Depression-Dejection; Anger-Hostility; Tension-Anixety; Vigor-Activity; Fatigue-Inertia; and Confusion-Bewilderment. In addition to individual factor scores, a Total Mood Disturbance Score is derived by combining the scores across all six factors.

TREATMENT RESULTS

As indicated in Table 2, the average duration of receipt of naltrexone was 6.0 weeks, with a range of less than one week to 21 weeks.

TABLE 2

Table 2. Duration of Receipt of Naltrexone May 1, 1976)

Number of Subjects	Interval (Days)
4	0 - 7
6	8 -21
4	22 - 56
6	57 - 147
	Mean: 42 days (6.0 weeks)
Total 20	Median: 24.5 days (3.5 weeks)

This duration contrasts with treatment duration of two other opioid-addicted populations (methadone maintenance and drug abstinent patients) who were treated in the Outpatient Service of the Washingtonian Center for Addictions at the same time as the naltrexone patients. Methadone maintenance patients remained in treatment an average of 22.4 weeks, while drug abstinent patients remained in treatment an average of 2.0 weeks.

Analysis of patient data from the Profile of Mood States, the Symptom Check List, and the Minnesota Multiphasic Personality Inventory was limited by the small number of patients (n=20) and the sequential termination of patients from the program (n=10 after three weeks of naltrexone treatment). Breakdown of patient scores on these measures according to length of stay on the program, however, indicates that the patients who continue on naltrexone the longest show less baseline psychopathology, less baseline mood disturbance, and fewer baseline symptoms than patients dropping out within the first two weeks. Later follow-up of both groups indicates that the patients who continued in naltrexone treatment longest were more likely to be employed and less likely to be addicted as of May 1, 1976.

These findings are consistent with data on other methods of treatment, which indicate that psychologically healthier patients continue longer and have more positive outcomes in treatment than less psychologically healthy patients.

Project staff currently have direct contact or reliable, although incomplete, information on 75% (15) of the 20 patients who have participated in the study. Table 3 indicates the current addiction status of all subjects, as of May 1, 1976. Three patients are currently receiving naltrexone and are drug-free: and seven who are not currently receiving naltrexone are known to be drug-free, so that ten (50%) are currently drug-free; three (15%) are known to be readdicted; one 5%) is deceased* and the status of 6 (30%) is unknown.

Of the seventeen subjects no longer receiving naltrexone, twelve (70%) remained in abstinence treatment after they stopped taking naltrexone. These 12 patients remained in treatment after cessation of naltrexone an average of 5.3 weeks, an average of 0.7 weeks less than they had been in naltrexone treatment. In addition, 12 of 19 (63%) remaining patients were known to be employed on May 1, 1976, compared with three of 20 (15%) patients employed at the onset of treatment.

Repeated physical and neurological examinations, electrocardiograms, blood hematology and chemistries, as well as

**Death occurred 80 days after last naltrexone dose. The medical examiner's opinion was related to complications of rheumatic heart disease, probably an arrhythmia.*

TABLE 3

Table 3. Current Addiction Status of Naltrexone Subjects (May 1, 1976)

Current Addiction Status	Number of Subjects
Abstinent (receiving naltrexone)	3
Abstinent (not receiving naltrexone)	7
Deceased (80 days after cessation of naltrexone	1
Readdicted	3
Unknown	6
Total	20

analysis of patient histories and symptom check list, do not reveal any toxic effects which can be attributed to naltrexone.

CLINICAL ISSUES: NALTREXONE AND ADDICTION TREATMENT

Many addicts become overwhelmed in the absence of external supports and controls. The naltrexone is an external control against the impulse and possibly the desire to use heroin, a control which our patients value, but about which all are ambivalent.

Initially almost all issues of control are focused on the power of the drug, naltrexone, to counteract the effects of heroin. Some patients want to explore the "power" of this external control against the powerful heroin. They report that they experiment early in their treatment to test the effectiveness of the antagonist. Typically, this is done in a systematic fashion, almost as if they need to quantify the drug's effect. For example, one patient purchased a large quantity of heroin and offered to share it with two of his friends, 24, 36, and 48 hours after his last dosage of naltrexone. After witnessing his friends inject the heroin at each of these points in time and verifying with them that they were high, he then tried to shoot up himself. He reported to us that he did not experience any opioid effects until the 48th hour and that at that point he experienced what he felt was a minimal effect.

The majority of our patients have self-tested the effectiveness of the drug, although not always in the methodical manner described above. only one such test, all of them are convinced that the drug is effective and most discontinue all opioid testing. Whether or not the effectiveness of the naltrexone blockade is tested by the patients, the belief is established early in treatment that the antagonist completely protects against the heroin high.

Once they are convinced of the drug's effectiveness many patients experience an initial reduction in the desire for heroin and a marked decrease in obsessional thinking about heroin acquisition and the heroin high. For some patients this initial reaction is short-lived and there is a resurgence of obsessive thinking about heroin or, similarly, of phobic thinking about the abstinence state, often accompanied by extreme fears of never again being able to get high. Some patients, disillusioned that the naltrexone did not eliminate their thoughts about heroin, terminate naltrexone treatment at this time. For the patients who remain on naltrexone the balance between the wish to get high and the fear of abstinence can be a continuing issue, although the conflict may diminish in intensity.

Another phenomenon observed is that, usually within the first 3-4 weeks on naltrexone, many patients begin to test out the necessity of using naltrexone as an external control against the desire to use heroin. In an attempt to achieve a balance between the external control afforded by the drug and their own internal controls, some wait until the moment before the clinic closes before running in to get their daily naltrexone. Others miss clinic appointments to see if they can abstain from heroin, for a brief period of time, without naltrexone.

One patient, for example, for the first two months on the program, attended clinic nearly every day. Later, he began to reject this external control by developing a pattern of skipping naltrexcne doses on weekends. He connected this behavior with his fear of becoming too dependent on the naltrexone and on the clinic structure, and with his wish to test out whether or not he would use heroin if he did not take the naltrexone. He was gravitating toward wanting to exercise complete control internally, at least part of the time. On these weekends, however, he managed to remain abstinent by believing, as he reported, that the naltrexone effect really lasted more than 24 hours.

Some patients attempt to use external control other than naltrexone; controls over which they feel they have more power than over naltrexone. Some are controls they used to attempt to remain abstinent from heroin in the past when they were not taking naltrexone. For example, they may leave the city for a day or lock themselves in their house to avoid temptation. It is as if they attempt to show that they, alone, without the help of the naltrexone, can exercise adequate control over the urge to use heroin.

As treatment and length of naltrexone use progresses, some patients realize that they can exercise partial control themselves, rather than depending entirely upon the external control, naltrexone. Many are conscious of their participation in establishing the balance between external and internal controls. One patient stated, for example, that he now found it unnecessary to "change everything at once". Energy was available for uses other than either total control or lack thereof, and the impact of "external circumstances" was reduced, allowing him to introspect and make decisions about his behavior, thoughts, and feelings.

The use of naltrexone reduces the fear that external environmental factors will cause a loss of control. After "testing" themselves in a non-drug environment on weekends, patients further become aware that they can also be on the street, in the places where they normally would take heroin, without taking heroin. This enlargement of the non-threatening, formerly self-destructive life space allows patients to feel freer. The patients who stayed in treatment for the longer periods of time progressed from missing naltrexone on weekends to missing doses occasionally during the week.

Further evidence of this greater sense of freedom and internal control is evidenced by patients' statements that they have more opportunities to develop self control with naltrexone treatment than they had with a therapeutic community or with methadone maintenance treatment. One patient, for example, a graduate of both methadone and therapeutic community alternatives, reported that the narcotic antagonist treatment approach was the first treatment approach in which he did not feel that he had to belittle himself and to keep his thoughts and feelings about the staff and other patients under control. He felt that in this treatment alternative the staff did not have anything "to hold over his head". Additionally, he felt he could do as he wished with regard to the continuance or noncontinuance of his treatment without experiencing the ill effects of either methadone detoxification or expulsion from the extended family atmosphere of a therapeutic community.

This same patient reported also that in the past he was never able to express any anger to program staff until it had built up to the point. of explosion. While on naltrexone, he was more aware, open, and in control of his feelings of annoyance and anger. In contrast to over-control of his feelings or exploding in an uncontrolled manner, he confronted the staff and told them what he found annoying. When the staff reacted by changing their own behaviors toward him, he reported that this was the first time that he had expressed anger and achieved a positive effect on others.

Staff, of course, must be constantly alert, as in the last example, to the patient's need for balance between external and internal controls. They must help the patient learn that thev will not be punished for continuing attempts at self-control such as missing clinic appointments. Rather, they must be allowed the latitude to acquire a balance between external and internal controls, without painful or damaging consequences. In fact, it is our impression that patients who remain abstinent following cessation of naltrexone treatment are those who are best able to achieve internalization

of control.

In summary, naltrexone treatment attracts a small subpopulation of the addict population who remain in treatment with the drug for a shorter duration than our methadone maintenance patients but longer than our drug abstinent outpatients.

No demonstrable toxicity from the drug has been demonstrated. Seventy percent of our naltrexone project patients remained in abstinent outpatient therapy after they stopped taking naltrexone; 50% are known to be currently drug-free: and 63% are currently employed. Clinical evaluation of the patients receiving naltrexone suggests that the experience of control over the urge to take heroin and over themselves is a major concomitant of the use of naltrexone. Ingestion of naltrexone provides a degree of external control, reducing the preoccupation with heroin and releasing energy for the pursuit of other goals.

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AN ANALYSIS OF NALTREXONE USE-ITS EFFICACY SAFETY AND POTENTIAL

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CLINICAL SETTING

The Buffalo Naltrexone Project is located in the 500 bed county hospitai, which is one of the affiliated hospitals of the State Universitv of New York's Medical School in Buffalo. This program operates within the Department of Psychiatry where the Emergency Drug Abuse Service and other drug related research programs are also located.

PATIENT SELECTION

Patients treated within the hospital for problems of substance abuse, excluding alcohol, are representative of the patients who were interviewed for or inducted onto naltrexone. The data presented covers the period from June 1974 through May 1976, a total of 24 months. Table I shows the usual race, age and sex distribution. Of a total of 42 patients who received naltrexone, four came from methadone maintenance, two were inducted prior to release from jail, three came from the V.A. Hospital drug program in a drug-free state and 33 came directly from street heroin use.

RECRUITMENT

The problem of recruitment in our community is ever present. In spite of more than adequate media coverage, including 'radio, television and newspapers, there was initially a reluctance to participate because of the experimental nature

TABLE 1

CHARACTERISTIC	N=42	%
Race		
black	32	76.1
Caucasian	5	11.9
Puerto Rican	4	9.5
Amer. Indian	1	2.5
Age		
20	1	2.4
21-29	14	33.3
30-39	15	35.7
40-49	11	26.2
50-59	1	2.4
Sex		
male	39	92.9
female	3	7.1

of the medication. In a small addict community such as ours (the best estimate is somewhere in the neighborhood of 2,000) this type of adverse comment spreads rapidly. Although this criticism has receded with time, the present disenchantment with methadone and the tendency to equate methadone and naltrexone present recruitment problems.

It appears that constant and repetitive media exposure should be a greater priority in recruitment than attempting to enlist patient referrals from methadone oriented programs, since a reluctance of methadone maintenance programs to refer patients for narcotic antagonist treatment has been apparent. Ultimately, however, there should be no problem in attracting large numbers to naltrexone once the drug is proven safe and released for general use.

CLINICAL EXPERIENCE

Of the 91 patients who were interviewed and screened for eligibility to participate in the naltrexone study, 42 were eventually given naltrexone. Table II delineates the various reasons the other 49 did not enter the study. It is no surprise that 32% of these patients had elevated liver iso enzyme values, and 22% opted for methadone maintenance treatment. As anticipated, the largest group of non-participants, 38.7% was comprised of those people who were lost to follow-up after initial screening. Generally, drug dependent patients are not well motivated to become drug free and are very skeptical of new treatment modalities.

In an attempt to determine the feasibility of outpatient induction and thereby the applicability of naltrexone administration to large groups of patients, 25 of the total 42 patients in the study were indeed inducted on an outpatient basis. Only 17 of these 25 patients were using heroin; the other 8 patients had already been detoxified from heroin while in jail or in other drug programs, and all 8 had remained drug free while on the street. Therefore, while a total of 25 patients were inducted on an outpatient basis, only 17 had to be treated in an outpatient ambulatory methadone detoxification program, remain drug free at least seven days, and then take naltrexone on a daily basis during the induction phase. Fifteen patients succeeded in completing that process and progressed to the three times per week dose stage while two patients dropped out of the study. Since the other eight patients had already been detoxified and had no problem in taking naltrexone, 23 of the 25 patients were successful in completing outpatient naltrexone induction. Refer to Table III.

TABLE 2

REJECTION CATEGORIES	N	%
Elevated liver iso enzyme value	16	32.6
Preferred methadone maintenance	11	22
Did not return following screening	19	38.7
Psychological problems exclusionary	2	4
Jailed	1	2

TABLE 3

Characteristic		N
Outpatient induction		25
Inpatient induction		17
Dose Range		
t.i.w.	150 - 150 - 150	4
	100 - 100 - 100	2
	200 - 200 - 200	1
	100 - 100 - 150	26
	50 - 50 - 75	1
Duration of naltrexone in days		
1- 7		11
8- 30		9
31 - 90		13
91 - 180		10
over 181		

A successful outpatient heroin detoxification and induction onto naltrexone of 92% of patients who chose that mode rather than hospitalization would auger well for the application of this mode to large numbers. However, it must be noted that an inordinate amount of staff support, beyond that which is normally available in most treatment programs, was expended in order to accomplish this high rate of success.

During the early months of the study some patients were placed on 200 mg. dose three times per week and a few were placed on a 100 mg. dose t.i.w. However, later on most patients were placed on 100, 100 and 150 mg. (Monday, Wednesday and Friday) and more recently, several patients have had a two times per week schedule (Tuesday and Friday) of 150 mg. each dose. Two patients have received a 50, 50, 75 mg. dose. Refer to Table III. Regardless of the dosage schedule, it has not, in any detectable manner, affected the patients' ability to remain drug free. Only one patient has expressed a feeling that he was not receiving enough naltrexone, an observation made relative to a vague feeling of uneasiness on Sundays following two weeks of 50 mg. t.i.w. This feeling disappeared when his Friday dose was increased 75 mg.

Table III also reveals the number of days of treatment.

It would appear that naltrexone is a drug that lends itself to wide flexibility in the manner and method of administration and is well suited to use in and by differing treatment philosophies. Dosage schedules and time intervals of administration are also fairly flexible.

Significant in our induction procedure was the administration to as many patients as possible of a battery of questionnaires and psychological test instruments. From these we hoped to obtain a profile of individuals who elect naltrexone and to determine whether or not they may significantly differ in personality, sociodemographic, or drug history characteristics from patients in other treatment modalities. This may be important for future selection of patients.

The data presented here are from 23 naltrexone patients who completed the Minnesota Multiphasic Personality Inventory (Hathaway and McKinley, 1951). 29 who completed the Beck Depression Inventory (Beck, Ward, Mendelson, Mock and Erbaugh, 1961), and from between 25 and 30 who completed various items on the Buffalo Inventory, a locally developed multi-purpose questionnaire which provides demographic and drug history information (Emergency Drug Abuse Service, revised, 1973). Our results are compared with those obtained in other studies. Because extensive information was available for a group of 163 male patients in methadone treatment (132 in a methadone maintenance program and 31 in methadone detoxification) who had completed the same instruments and because both groups came from the same community, particular attention was paid to the similarities and differences between these groups.

In taking this data into consideration, it must be noted that this is an exploratory study of a Small sample of naltrexone patients. The results are suggestive at best and must not be construed as definitive.

DEMOGRAPHIC AND DRUG HISTORY INFORMATION

The Buffalo Inventory is aimed at obtaining precise information concerning the patient's basic history, such as age and level of education, as well as measures of the severity of his drug addiction. Tables IV and V present the results for eight demographic variables and eight drug history variables thought to be of particular interest. It will be noted that differences between naltrexone and methadone patients are minimal except that, on the average, naltrexone patients appear to be a somewhat older group (34 years vs. 26 years) and the mean length of habit of naltrexone patients is 14.3 years in contrast to 5.8 years for methadone patients. While we have no certain explanation for this difference, our clinical impression is that older heroin users are more exhausted by the drug world "hustle" and are more amenable to becoming drug-free. Frequency of use of other drugs with heroin is very similar despite the difference in length of habit, but is somewhat less than we might have expected. Apart from age and length of habit, our drug history and demographic data do not appear to discriminate between patients choosing treatment with naltrexone and those choosing methadone treatment.

MINNESOTA MULTIPHASIC PERSONALITY INVENTORY

Probably the best known of all "objective" psychological test instruments and the one most widely used in the study of drug abusers, the MMPI consists of 550 true-false questions which yield ten clinical scales and four validity scales. Typically, addicts have been found to have elevations on the psychopathic deviate and hypomania scales. According to Hill, Haertzen and Glaser (1960), this 4-9 profile is indicative of "antisocial, amoral, impulsive, irritable, hostile and

TABLE 4

DEMOGRAPHIC CHARACTERISTICS OF NALTREXONE AND METHADONE MAINTENANCE PATIENTS

VARIABLE		NALTREXONE	N	METHADONE	N
mean age		34.47	30	26.63	163
race	Black	80.00%	30	56.44%	163
	Caucasian	10.00%,		43.562	
	Puerto Rican	10.00%		00.00%	
mean level of education (years)		10.93	30	11.57	159
longest stretch of employment (years)		4.65	28	3.14	146
youthful offenders		35.71%	28	47.17%	159
ever arrested for breaking law		79.31%	29	88.7%	160
currently have charges		10.71%	28	31.01%	161
presently on parole		10.00%;	30	5.00%	160

psychopathic" traits. Although it should be pointed out that some recent studies find a characteristic 2-4-8 pattern for the addict population (Berzins, Ross and English, 1974), the 4-9 pattern is regarded as "the profile of the social delinquent, alienated from society and likely to act out his resentment" (Burke and Eichberg, 1972).

Table VI presents the mean profile derived from 23 naltrexone patients who completed the MMPI and compares it with the profile for the methadone group and the composite adult addict profile in the classic Hill et al. study. Mean scores for the several MMPI scales for naltrexone and methadone patients are also separately shown on Table VII.

The naltrexone patient profile is very similar to that of Hill et al. except that the naltrexone profile is somewhat more elevated, and the naltrexone D (depression) score is markedly higher. When the naltrexone profile is further compared to profiles for subgroups which Hill et al. have labeled "psychopathic", "neurotic" and "schizoid" it is clear that naltrexone patients most closely resemble the psychopathic subgroup.

The 4-7-8 profile for the methadone patients is less characteristic of addict groups. This suggests that this particular methadone group may have more schizophrenic-like psychopathology than the naltrexone group. Overall, the naltrexone group appears more nearly "normal" than the methadone group, and indeed its scores on four scales (Hs, Pd, Pt and Sc) are significantly lower ($p < .001$).

BECK DEPRESSION INVENTORY

Used here as a self-report, this instrument consists of 21 items which reflect differing symptoms or characteristic features of depression. Each item involves a series of statements graduated in severity on a scale of 0 to 3. The respondent's total score thus depends both on the number of separate symptoms or features of depression he endorses and on the degree of severity indicated for each. Table VIII presents means and standard deviations for naltrexone and methadone patients and for three comparison samples. It will be seen that on the average the naltrexone group appears to be mildly depressed while the methadone maintenance group are characterized as not depressed according to Beck's norms. However, the difference between the naltrexone and methadone maintenance group was not statistically significant.

Furthermore, there was considerable variation in Beck scores among both groups, with scores of the naltrexone patients ranging from 0 to 27 at the time of induction. We were unable to demonstrate

TABLE 5

DRUG HISTORIES OF NALTREXONE AND METHADONE MAINTENANCE PATIENTS

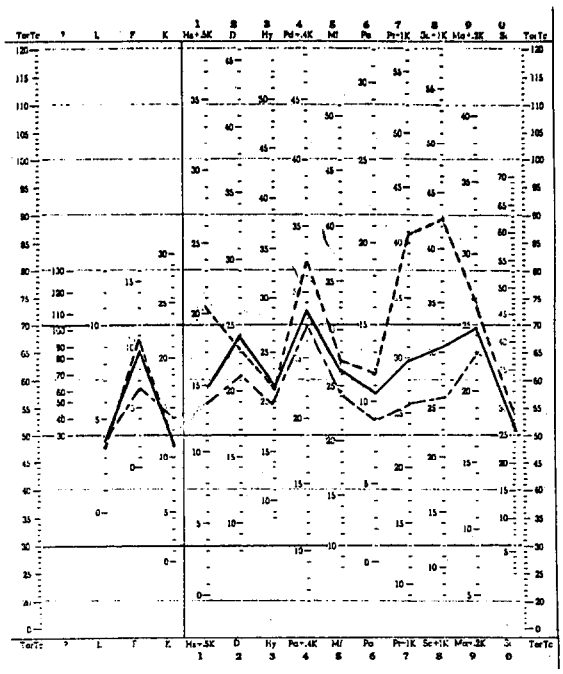
VARIABLE		NALTREXONE	N	METHADONE	N
length of habit (mean years)		14.30	30	5.82	163
use of heroin	daily	84.02%	26	94.30%	158
	2-3 times/week	11.54%		5.70%	
	weekends	3.85%		0.00%	
no. of sacks in cooker	one	19.23%	26	9.38%	160
	two	19.23%		39.38%	
	three	19.23%		24.38%	
	four	19.23%		14.38%	
	more than four	23.08%		12.50%	
use other drugs with heroin	daily	14,81%	27	14.74%	156
	2-3 times/week	7.41%		15.38%	
	rarely	48.155		42.31%	
	nover	29.63%		28.21%	
times tried to kick	never	3.85%	26	4,434	162
	once	15,384		17.28%	
	more than once	80,77%		78.40%	
times sought treatment	never	20.83%	24	17.07%	123
	one	16.67%		28.46%	
	two	12.50%		23.58%	
	three	0.00%		18.70%	
	four	16.67%		2.44%	
	more than four	33.33%		9.76%	
times in methadone detox.	never	20.00%	25	30.02%	123
	one	36.00%		29.27%	
	two	20.00%		19.51%	
	three	4.00%		8.13%	
	four	8.00%		.81%	
	more than four	12.00%		3.25%	
times in methadone maint.	never	36.00%	25	59.35%	123
	one	28.00%		32.52%	
	two	12.00%		6.50%	
	three	16.00%		1.63%	
	four	8.00%		0.00%	
	more than four	0.00%		0.00%	

any relationship between level of depression at induction and length of stay in naltrexone treatment, but the possibility cannot be ruled out that such a relationship might emerge if our sample size were larger.

ANALYSIS OF DRUG SAFETY

To determine adverse effects of naltrexone on patients, the laboratory data performed on all subjects was reviewed. An analysis of blood pressure readings by the "t" test for related measures was performed to determine whether there

TABLE 6



MMPI profiles: ------ Naltrexone (N=23; males)
- - - - - Maintenance (N=106; males)
— · — · — former narcotic addicts from Lexington, Ky.

TABLE 7

MEAN MMPI SCORES (WITH K CORRECTION) FOR NALTREXONE .AND METHADONE MAINTENANCE PATIENTS

SCALES	NALTREXONE	METHADONE
L	3.96	3.58
F	9.65	10.84
K	11.61	11.36
Hs	14.85	21.49
D	24.04	23.07
Hy	21.70	21.44
Pd	28.47	32.26
Mf	26.13	27.25
Pa	10.57	11.78
Pt	29.83	40.75
Sc	30.26	42.89
Ma	24.80	26.53
Si	26.70	29.25

was a significant difference between the induction and later treatment blood pressures. Because of insufficient data or initial hypertension, only 13 patients were used in the analysis. There was no significant increase in systolic or diastolic values during treatment by this analysis in the 13 patients.

A continuing problem was the occurrence of elevated liver iso enzyme values involving SGOT, SGPT or alkaline phosphatase. Nine patients had elevated values at various times. In each case, patients admitted to excess alcohol intake, and with cessation of drinking, iso enzyme values began decreasing toward normal values. Two patients who had values five times normal were given placebo naltrexone for 30 days with no change in values, until they seriously undertook to stop all alcohol intake. Following that, once again all levels began to decline toward normal values. It is very difficult in this type of patient population to determine the effect of naltrexone on the liver (antecedent effects of drugs and concomitant excess alcohol intake).

Fourteen percent of the patients showed a relative increase in lymphocyte counts during treatment. This unexpected result indicates a possible area of investigation to determine whether naltrexone does influence lymphocyte counts.

In all other parameters studied including serial EKG, urinalysis, SMA 14 and monthly physical exam, no evidence of adverse effects attributable to naltrexone were noted.

Why did patients who were taking naltrexone on a regular basis stop? Table IX lists the various reasons, and of interest is the only real and continuing complaint involving the taking of naltrexone that has surfaced throughout the 24 months of the study. Fourteen patients complained of abdominal distress following the taking of naltrexone. The complaint of gastric upset, pain, cramping and belching persisted in spite of antacids, food intake prior to medication and a decrease in the mg. dose of naltrexone. This was either the primary or secondary reason given by eight patients for finally deciding to terminate themselves from the study.

NALTREXONE POTENTIAL

What place do we envision for naltrexone in the future? At present, the chemotherapeutic treatment for opiate drug dependence has relied solely upon methadone, either in maintenance or detoxification. Naltrexone, a narcotic antagonist, with proven safety, flexibility and a high degree of efficacy, provides a much needed addition to the chemotherapeutic treatment approach.

Our clinical experience strongly suggests that patient selection is of paramount importance in predicting successful treatment with naltrexone. We have shown that demographic and prior drug history variables hold little promise for differential selection, nor do those psychological test scores we have examined to date appear to be useful for prediction. Nevertheless, it is our distinct impression that motivation is a major factor not only initially but throughout treatment. This is particularly true since the taking of naltrexone, in contrast to methadone, offers no gratification in itself nor does it have a negative recruitment effect. Truly, therefore, naltrexone presents a treatment modality for those opiate drug dependent persons highly motivated to become drug free.

Despite our findings of safety and efficacy of naltrexone, the method of naltrexone induction presents a problem which is an important consideration. Because of its antagonistic action producing the abstinence syndrome, inpatient detoxification and induction is the preferred treatment. However, the extrapolation of this method to large numbers of patients is precluded by consideration of economic factors and stress on other resources.

Our experience has demonstrated a high degree of success in outpatient induction. The limiting factors we see are the small number of inductions that can be handled at one time and the inordinate amount of staff support required for successful treatment from beginning to end.

While there is no question of the potential of naltrexone for treatment of opiate drug dependency, it must, like other treatment modalities, be deployed selectively.

TABLE 8

BECK DEPRESSION INVENTORY: MEANS AND STANDARD DEVIATIONS

SAMPLE	SEX	N	MEAN	SD
naltrexone	M	29	13.00	8.80
methadone maintenance (Plumb, D'Amanda, & Taintor, 1975)	M	163	9.79	6.24
Phoenix House inductees (DeLeon, Skodol, & Rosenthal, 1973	M-F	38	23.24	9.36
hospital inpatient (Beck, 1961)	M-F	153	6.51	9.65
Beck norms:				
no depression	M-F	115	10.9	8.1
mild depression	M-F	127	18.7	10.2
moderate depression	M-F	134	25.4	9.6
severe depression	M-F	133	30.0	10.6

TABLE 9

PRIMARY REASON FOR DISCONTNUING NALTREXONE	N = 33	SECONDARY REASON
1. Hepatitis - not related to naltrexone	2	
2. treatment success - patient and staff decision	7	
3. patient felt he no longer needed naltrexone	3	
4. could not tolerate inpatient hospital stay on psychiatric ward	1	
5. peer group pressure to return to drug use, wanted to return to drug use, abusing other drugs, alcoholic	3	1 #10
6. gave no reason	7	2 #10
7. left town	4	2 #10
8. jail	1	
9. wanted methadone maintenance	1	
10. complained of stomach distress	3	1 #5
11. thought naltrexone made him sick	1	

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ACKNOWLEDGMENT

*NIMH Contract HSM4273259ND

CLINICAL EFFICACY OF NALTREXONE: A ONE YEAR FOLLOW UP

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Our research on naltrexone, beginning in 1973, focused initially on the pharmacology of the drug as a prelude to investigating its clinical efficacy in treating narcotic addition. We explored naltrexone's safety, toxicity, side-effects, antagonism to heroin, and pharmacokinetics (Resnick et al., 1974; Volavka et al., 1975; Verebely et al., 1976; Volavka et al., 1976). Our studies of naltrexone's clinical efficacy have focused mainly on isolating from a wealth of demographic, psychosocial, and drug history data, factors which may serve as reliable predictors of treatment outcome. From this study we hoped to determine a description of those individuals most likely to benefit from treatment with naltrexone.

The data was obtained at intake and correlated with treatment outcome at 12 months. Based on earlier retrospective studies using cyclazocine, (Resnick et al., 1970; Resnick et al., 1971) and on our clinical impressions, we formulated the hypothesis that heroin addicts treated with naltrexone who were opiate-free at 12 months after entering treatment would more likely 1) have more years of addiction: 2) have a higher capacity for object relations; 3) show higher levels of psychosocial functioning; and 4) have histories of longer opiate-free periods during the course of their addiction than those who become re-addicted.

METHOD

An extensive battery of information was obtained at intake and subsequently was reviewed for accuracy for patients who remained in treatment. If a patient met medical and other criteria for receiving naltrexone he was detoxified from opiates

and remained opiate-free for a 5-10 day period before naltrexone was started. Naltrexone was dispensed in the clinic, usually 3 times/week, with no take home doses. Each patient was assigned a primary therapist who provided ancillary services and who monitored his clinical course. Twelve months after receiving the first naltrexone dose, patients were categorized as beinq opiate-free or opiate-dependent. This judgment was made by staff consensus on the basis of their continued contact with patients and/or their friends and relatives, urinalysis and Narcan tests.

RESULTS

Of the 81 patients, 27 were opiate-free (33%) and 54 were opiate-dependent (67%) one year after starting naltrexone. Thirteen of the 54 opiate-dependent patients were enrolled in a methadone maintenance treatment program. A comparison of selected intake parameters for the opiate-free and the opiate-dependent patients at one year after starting treatment is shown in Table 2.

TABLE 1

NUMBER OF SUCCESSIVE APPLICANTS FOR NALTREXONE TREATMENT MAY 1, 1974 - FEBRUARY 28, 1975	191
EXCLUDED FROM STUDY:	110
Medical and/or Psychiatric Ineligibility	2
Transfers from Cyclazocine	4
Unable to Complete Detoxification	66
Took Naltrexone Less Than One Week	38
STUDY GROUP EVALUATED FOR TREATMENT OUTCOME	81

Table 1 shows how we arrived at the study sample. There were 191 successive applicants over 10 months on whom intake information was obtained Of this total population, 110 were excluded from the study sample as shown in the Table: two were excluded for medical and/or psychiatric ineligibility; four were transfers from cyclazocine without having an interim period of readdiction; sixty-six were unable to complete detoxification and never started naltrexone; and thirty-eight took naltrexone less than one week, i.e. only one or two doses. This latter group either 1) stopped medication because of initial side-effects that they found unacceptable (these were usually due to symptoms of precipitated abstinence); or 2) they did not wish to receive this treatment, and requested naltrexone for an ulterior purpose, usually to gain admission to the hospital, since methadone maintenance or detoxification alone was not provided in our facility. The study group was comprised of 81 individuals who received naltrexone for one week or longer.

TABLE 2

COMPARISON OF PATIENTS OPIATE-FREE AND OPIATE-DEPENDENT AT TWELVE MONTHS

	INTAKE PARAMETER	OPIATE FREE N=27	OPIATE DEPENDENT N=54	p
	DRUG HISTORY			
1.	Age at intake	26.2	27.0	n.s.
2.	Age 1st opiate use	17.5	19.4	n.s.
3.	Age addicted opiates	18.6	20.8	n.s.
4.	# years addicted opiates	8.4	6.9	n.s.
5.	Mean $ used daily 6 mos. prior	6.61	15.0	n.s.
6.	Longest clean NYC (mos.)	5.83	3.8	n.s.
	PSYCHOSOCIAL			
7.	Current employment (fulltime)	54%	53%	n.s.
8.	Married or commonlaw *	40%	25%	n.s.
9.	Has current relationship	50%	57%	n.s.
10.	Education (yrs.)**	11.44	11.29	n.s.
	NALTREXONE			
11.	Weeks on naltrexone	12.1	6.8	<.01

* N=19 for opiate-free: N=32 for opiate-dependent

** N=8 for opiate-free, N=22 for opiate-dependent

Consistent with our hypothesis, the opiate-free as compared to the opiate-dependent group at 12 months had been addicted for a greater number of years, had shown at intake a lower level of opiate dependence according to money spent for opiates during preceding months, had a history of longer opiate-free periods interspersed during the course of addiction, and were better able to maintain a marital relationship. These differences, however, were not statistically significant.

The number of weeks that patients took naltrexone did significantly differentiate opiate-free from opiate-dependent patients at 12 months. Other findings were that 1) relapsing patients tended to come back to treatment and stay for longer periods of time -- the mean number of days on naltrexone during the first episode of treatment for patients who relapsed to opiate use and then came back to treatment was 30 days, while during the second treatment episode it was 85 days; and 2) the proportion of patients in either the opiate-free or opiate-dependent groups at any one time was essentially stabilized after 6 months, although individual patients shifted between the two groups during the study period. In other words, outcome (in terms of opiate-free or opiate-dependent status) assessed at 9, 12 and 15 months, in each case using the same patient population, showed a constant ratio of number of opiate-free to opiate-dependent patients

TABLE 3

COMPARISON OF PATIENTS ON NALTREXONE AT LEAST ONE WEEK AND PATIENTS UNABLE TO COMPLETE DETOXIFICATION

INTAKE PARAMETER	ON NALTREXONE AT LEAST ONE WEEK N=81	NEVER COMPLETED DETOXIFICATION N=38	p
DRUG HISTORY			
1. Age at intake	26.7	26.29	n.s.
2. Age 1st opiate use	18.8	17.59	n.s.
3. Age addicted opiates	20.07	19.29	n.s.
4. # years addicted	7.40	7.34	n.s.
5. Mean $ daily 6 mos. prior	12.20	52.87	$p < .01$
6. Longest clean NYC (mos)	4.48	5.21	n.s.
PSYCHOSOCIAL			
7. Current employment	53%	29%	n.s.
8. Has current relationship	55%	74%	n.s.
9. Education*	11.33	10.97	n.s.

* N=30 for one week on naltrexone group.

although the individuals comprising the two groups shifted back and forth from opiate-free to opiate-dependent status during the course of the study.

We looked also for possible differences between patients who received naltrexone for at least one week (N=81) and those who never completed detoxification (N=38). Table 3 compares psychosocial factors for these two patient groups. One outstanding difference between the groups is that the mean amount of opiates used during the 6 months prior to treatment was significantly larger for patients who did not complete detoxification (i.e. never received naltrexone). Another is that nearly twice as many subjects who took naltrexone for at least one week were employed at the time of intake as compared to subjects who did not successfully detoxify.

DISCUSSION

The present study explored whether patient characteristics identifiable at intake correlate with treatment outcome and can be used to delineate candidates most likely to benefit from treatment with naltrexone. In prior studies, we addressed the question of who would most likely benefit from cyclazocine. Descriptive criteria that could identify such patients were found (Resnick et al., 1970), but a subsequent study showed that the patients self-selection of treatment modality correlated equally well with retention and outcome (Resnick et al., 1971). In our current study we were not able to determine for whom naltrexone treatment is most helpful among patients who self-select this treatment.

The present study did find that time on naltrexone significantly differentiated opiate-free from opiate-dependent patients at 12 months. This finding suggests that naltrexone contributes to a favorable outcome as the time in treatment increases. A critical efficacy issue, therefore, is to assess factors that aid in preventing patients from dropping treatment prematurely. In the absence of identifiable predisposing variables associated with remaining in treatment, we considered whether non-pharmacologic treatment factors may have affected patient retention and outcome. We believe that the efficacy of naltrexone in this study was related to staff ability to involve patients in counseling and to patients' capacity to respond. We did not, however, isolate or control for these treatment variables. They could not be assessed adequately in retrospect.

Therefore, we are planning a study of naltrexone efficacy in which individual psychotherapy is the dependent variable and is compared to intervention that includes medical care and concrete services only. This study will ask 1) whether outcome differs between groups receiving naltrexone alone or naltrexone plus individual psychotherapy: and 2) what factors contribute to the length of time that a patient takes naltrexone once he has started when the variable of individual psychotherapy is controlled for. Our hypothesis is that psychotherapeutic intervention will have a positive effect on patients remaining in treatment and progressing toward rehabilitation. The literature has no reports of systematic assessments of this hypothesis. Information derived from the projected study will help provide indications for the most appropriate clinical setting for using naltrexone.

Finally, our finding that relapsing patients tended to remain in treatment longer with each successive readmission suggests that evaluations of efficacy will require a follow-up period of longer than one year.

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THE NIDA BEHAVIORAL STUDIES

THE THEORETICAL BASIS OF NARCOTIC ADDICTION TREATMENT WITH NARCOTIC ANTAGONISTS

Abraham Wikler, M.D.

The theoretical basis of narcotic addiction treatment with narcotic antagonists was well stated by Martin et al. (1966). Briefly, out-patient maintenance of a previously detoxified opioid addict on a daily oral opioid-blocking dose of a narcotic antagonist is expected to accomplish two objectives: (a) to remove the incentive for seeking and using opioid drugs; and (b), to extinguish conditioned abstinence (including "craving") should this phenomenon occur as a response to environmental stimuli to which unconditioned abstinence had previously become conditioned (Wikler, 1948; 1965). Needless to add, such a period of out-patient maintenance on a narcotic antagonist should be used to "rehabilitate" the patient - i.e., to train him in the skills necessary for holding a socially useful iob. to form new, mutually supportive relationships with non-drug using persons, and to persuade him to give up the illegal "hustling" activities which had become self-reinforcing during previous periods of opioid addiction. Such a period of out-patient maintenance on a narcotic antagonist would have advantages over detoxification followed by enforced abstention from opioids (by prison sentences with or without a subsequent probationary period) in that it would permit the patient to expose himself to conditional environmental stimuli which evoke "craving" and possibly other conditioned abstinence phenomena, without the danger of their reinforcement by the pharmacological actions of opioid drugs. Eventually, if the patient so exposes himself frequently enough, such conditioned abstinence phenomena should become extinguished through repeated non-reinforcement.

Emphasizing the importance of extinction of conditioned abstinence and of drug-seeking behavior for minimizing the probability of relapse after out-patient maintenance on the narcotic antagonist has been discontinued, Wikler (1974) proposed a program of " active extinction," to be carried out initially while the patient is still an in-patient at the hospital (where he was detoxified) and subsequently as an out-patient on narcotic antagonist maintenance. Along the lines of

the models used to extinguish conditioned responses and behavior in animal experimentation, it was suggested that as in-patients, previously detoxified patients blocked by a narcotic antagonist be exposed to conditioned stimuli that evoke "craving" and perhaps other conditioned abstinence phenomena and be permitted to self-inject themselves with heroin repeatedly ad libitum: hopefully, under narcotic-antagonist blockade, self-injection of heroin-would ultimately cease. Appropriate conditioned stimuli might consist of heroin-related pictures (Teasdale, 1973) or the presence of previously detoxified patients self-injecting themselves with heroin in the unblocked condition. After completion of such active extinction under narcotic antagonist blockade as an in-patient, the patient may go on out-patient status, still receiving his daily oral blocking dose of the narcotic antagonist. It was assumed that under the different conditions of out-patient status, the patient would again display opioid-seeking behavior, which should not be discouraged, as further extinction of this behavior under "natural" conditions is to be desired. The progress of such patient-regulated "hustling" for and extinction of opioid-seeking behavior could be monitored by frequent, though unscheduled urine-testing for morphine. It was suggested that maintenance on a narcotic antagonist should be continued for about 10 months to one year (beyond the duration of protracted abstinence, which lasts about 30 weeks, Martin and Jasinski, 1969) and if urine screen remains negative for morphine, the narcotic antagonist could then be discontinued. Conditioned abstinence and opioid-seeking behavior having been extinguished, and the patient having been "rehabilitated," the probability of relapse would be greatly reduced.

That in the rat well-established intravenous morphine self-injection can be extinguished by pre-treatment with naloxone and presentation of a conditioned reinforcer in the operant chamber has been demonstrated by Davis and Smith (1974). There is some question of whether in this study the decline in lever-pressing for morphine was not due to aversive conditioning, rather than to extinction, inasmuch as after pre-treatment with naloxone, no transient increase in lever pressing rate was observed prior to the rapid fall in lever-pressing rate. Naloxone may have precipitated a grossly undetectable abstinence syndrome, inasmuch as the rats had been self-injecting morphine, albeit in a very small unit dose, 60 mcg/kg, for 3 days prior to naloxone pre- treatment. However! in other intravenous morphine self-injecting rats, apparent extinction was accomplished by substituting saline for morphine solution in the operant chamber and presentation of the conditioned reinforcer; no transient increase in lever-pressing rate was observed under these conditions either.

As might have been anticipated, however, carrying out active extinction in man presents special problems because of his cognitive ability to perceive the experimental arrangements and alternative courses of action open to him which even the experimenter could not foresee. From as yet unpublished reports, it appears that these are two major problems connected with attempts at in-patient extinction with the aid of narcotic antagonists: (a) the patient simply refuses to self-inject himself with heroin or another opioid while he is blockaded by a narcotic antagonist, on the grounds that he "knows that he will not get high;" and (b) the patient reports that the narcotic antagonist "took all my craving" away - i.e. , the narcotic antagonist seems to have a "satiating" effect.

The question of whether or not the opioid antagonists exert a hitherto unknown agonistic, "satiating" effect on opioid-deprived receptors is very important from both the theoretical and practical standpoints. If a placebo can be found which produces an unpleasant after- taste similar to that produced by naltrexone, then a double-blind experiment on initiation of self-injection with heroin or hydromorphone may answer this question. If affirmed, a "satiation" effect of an opioid antagonist would render extinction trials both impractical and useless. Then reliance will have to be made on prolonged, though limited maintenance on an opioid-antagonist with, of course, efforts at re-education and social rehabilitation (which would be necessary in any case). However, should the results of such an experiment be negative - i.e., naltrexone does not have a "satiating" effect, then perhaps it may be possible to modify the extinction procedure in such a way as to make experimental extinction possible, despite the addict's learned discrimination (his prior knowledge that naltrexone will block heroin effects, including "euphoria") . For example, an addict may be admitted to the hospital and "detoxified." Then he may be allowed to work for and self-inject "earned" heroin (amounts subject to specified limits) on one day. Three or four days later, a "naloxone test" is made to determine if there is any residual physical dependence,

and if the results are positive, "naloxone tests" are repeated every three days until the results are negative. Then naltrexone placebo (with the metallic after-taste) is administered by mouth and again the addict is permitted or persuaded (by monetary reinforcement, if necessary) to work for and self-inject "earned" heroin. Following this, "naloxone tests" are made as before until the results are negative (or, the data from the previous "naloxone tests" may be accepted as an estimate of the time required for physical dependence to dissipate). Then a full 24-hour blocking dose of naltrexone is administered by month and the subject is again permitted or persuaded (by monetary reinforcement, if necessary) to work for and self-inject "earned" heroin. Thereafter. the full 24-hour blocking dose of naltrexone is administered by mouth every day and the extinction procedure is repeated until the addict no longer works for and self-injects heroin. For other addicts, the naltrexone placebo day should be omitted, attempted extinction (by monetary reinforcement , if necessary) being carried out under full 24-hour blocking doses of naltrexone. This is necessary to insure that addicts will not be able to anticipate whether or not the oral medication on the first day will block the effects of self-injected heroin. Or, another method may be tried. On the first day, the "detoxified" addict is given a partial blocking dose of naltrexone p.o., and he is permitted to work for and receive heroin on that day. At intervals determined by negative "naloxone tests" for physical dependence that may have been acquired by self-injection of heroin, the procedure is repeated with progressively increasing doses of naltrexone p.o., up to and including the day (or days) on which a full 24-hour blocking dose of naltrexone is administered and the addict finally ceases to self-inject himself with heroin [despite monetary reinforcement). It may be expected that the proposed program will have to be modified to nullify unforeseen, ingenious methods which the addicts may employ to "decode" the oral medication conditions. At any rate, by going "Beyond Skinner" (anticipating what the addict may do to discriminate naltrexone placebo from naltrexone) it should be possible to achieve experimental extinction of heroin-seeking behavior under hospital conditions.

Flexibility and ingenuity is also necessary in the maintenance of a patient on a narcotic antagonist in out-patient status. A close personal relationship between the patient and therapist is essential. The elements of conditioning theory, conditioned abstinence and "craving" as well as conditioned "hustling" should be explained to the patient, so that he could recognize these phenomena for what they are, rather than ascribe them to the "flu." After out-patient extinction has proceeded, the relationship between the therapist and the patient should be such that the therapist can furnish positive reinforcement for socially acceptable behaviors. Quitting naltrexone or other narcotic antagonist should be expected, but the relationship between therapist and patient should be maintained nevertheless-and every effort should be made to brine the patient back into the narcotic antagonist-extinction treatment program without prejudice. In short, it should be remembered that a clinic is very different from an animal operant chamber and that in man, unlike the rat and monkey, the experimenter has met his match. Nevertheless, the principles of conditioning and extinction still hold - it is up to the experimenter to modify the animal paradigm of active extinction in a manner that will resolve the difficulties created by the patient's powers of discrimination of the stimulus and reinforcement conditions set up by the experimenter.

Addendum: If it is proven that narcotic antagonists do have a "satiating" effect, then extinction of conditioned abstinence may be carried out as follows. Admit a group of detoxified addicts to the hospital and have them sign a contract (with monetary rewards) to stay in the hospital at least one month regardless of whether or not they are permitted to self- inject heroin. Do not administer any opioid antagonist. Allow some of the subjects to self-inject heroin without narcotic antagonist-blockade, while the others are not permitted to self-inject anything. Watching fellow-subjects self-inject heroin without being able to do likewise is likely to evoke strong "craving" and other signs and/or symptoms of conditioned abstinence which, on daily repetition should gradually wane and eventually extinguish. Then these subjects should be placed on full blocking doses of naltrexone and discharged to out-patient status where extinction of heroin-seeking behavior may take place if daily naltrexone medication is maintained and the subject "hustles" for heroin or other opioids. New detoxified addicts should now be admitted to reform the hospital in-patient group and permitted to self-inject heroin without narcotic antagonist blockade, while those who had been allowed previously to self-inject heroin without blockade are now detoxified and then carried through the con-

ditioned abstinence extinction procedure, signing another contract if necessary. After these subjects are discharged to out-patient status on naltrexone, the in-patient group can be re-formed again by admission of new detoxified addicts, and the extinction and discharge sequence can be repeated indefinitely. For controls, some of the subjects who had been permitted to self-inject heroin without blockade may be detoxified and discharged to out-patient status on naltrexone without going through the conditioned abstinence extinction procedure.

ACKNOWLEDGMENT

Preparation of this article was supported, in part, by Research Grant No. DA 01131 from the National Institute on Drug Abuse.

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LIMITATATIONS OF AN EXTINCTION APPROACH TO NARCOTIC ANTAGONIST TREATMENT

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In a 1966 study, Martin proposed the use of cyclazocine in the long-term treatment of heroin addicts.(1) Wikler has proposed a behavioral program that would involve the active extinction of both classically conditioned abstinence and operantly conditioned self-administration of heroin by the patient who is using a narcotic antagonist.(2) While narcotic antagonists have been used in ambulatory settings for a number of years, Wikler's formulation remains the sole approach to narcotic antagonist treatment that is based solidly in theory and data from laboratory experiments on the one hand, while utilizing the special properties of narcotic antagonists on the other. Wikler's formulation is based upon the notion that stimuli previously paired with unconditioned abstinence symptoms will elicit the abstinence syndrome in opioid-free, former narcotics users. Under these circumstances, the ex-addict will readily relapse to heroin use in the presence of familiar environmental stimuli.(3) Wikler has proposed that in the presence of former associates and other relevant stimuli, the addict treated with narcotic antagonists will repeatedly challenge with opiates. In the process of his repeated blocked opioid administrations, extinction would be expected.(2) Because of the centrality of the extinction hypothesis to narcotic antagonist treatment of the narcotics user, it is important to review more recent data which may alter this formulation of narcotic antagonist treatment.

In defining "extinction," experimental psychologists have (it seems to me) been more vague than they have been in some other areas.(4) In its simplest form, extinction of food reinforced behavior in a hungry animal involves the following elements: 1) the stimulus properties of the environment (including the hungry animal) are similar to circumstances when the behavior was reinforced by food and 2) the conditions are such that the behavior can occur but reinforcement will not occur. The usual consequence of this condition is that the previously reinforced behavior will increase in frequency and amount prior to its elimination, and the threshold of aggressive behavior will

be lowered making aggressive behavior more likely.

In the opioid-dependent animal in the morphine self-administration paradigm, extinction of drug-seeking behavior will occur if saline is substituted for morphine as a reinforcer. (5) If low doses of naloxone are administered to an opioid-dependent animal, drug-seeking behavior will increase, presumably in response to precipitated abstinence.(6) Such behavior will be suppressed in the presence of high blocking doses of naloxone, since abstinence relief is impossible.(6) Extinction of the operant response in the opioid-dependent animal appears to occur. It is also clear that the behavior will readily be reestablished under conditions where reinforcement again consequates the behavior.

Extinction of classically conditioned autonomic responses occurs when a conditioned stimulus is repeatedly presented in the absence of the unconditioned stimulus. Under these circumstances, the autonomic response will no longer occur in response to the conditioned stimulus. Thus, Goldberg and Schuster observed rapid extinction of conditioned abstinence responses (associated with a red light).(7) In contrast, stimuli associated with morphine reinforcement (e.g., a red light present with each self-injection of morphine) acquired secondary reinforcing properties that persisted up to 19 days after complete withdrawal of morphine.(8) Like the red light in the experiment of Goldberg and Schuster, specific stimuli can be paired (in a classical conditioning paradigm) with previous episodes of drug withdrawal or narcotic antagonist administration in a dependent animal (conditioned abstinence). Specific stimuli may also be associated with the primary reinforcing properties of the drug, as described by Goldberg, Schuster, and Woods (8) and others. In the experiments of Smith and Davis (9), rats will work for the sound of the pump previously paired with repeated morphine administrations. In summary, in the operant paradigm, animals will "work" for opioids (or saline) in the presence of stimuli previously associated with drug availability, and will also "work" for conditioned reinforcers (i.e., stimuli) previously paired with morphine administration (e.g., the sound of the pump).

In the presence of stimuli associated with the previous unavailability of opioids, former addicts should operate under S^{Δ} conditions and not work for drug reinforcement (e.g., the Vietnam heroin user returned to the United States). By contrast, under stimulus conditions previously associated with drug availability, relapse is expected (S^{D}). As Wikler has pointed out, extinction will not take place in prisons and other drug-free institutions not previously associated with drug use (i.e., under conditions of drug unavailability).(3) The essential question that we have been attempting to define over three years in human and animal experiments with narcotic antagonists is whether behavior observed under narcotic antagonist administration is consistent with notions of extinction of operant and/or classical conditioning, or whether it is more consistent with other explanations (e.g., satiation, aversive conditioning, or discrimination leaming.(10, 11, 12, 13) The question has important implications not only in terms of the approach that treatment programs may take with individual patients, but it is also of importance in terms of the optimal length of treatment with narcotic antagonists and the manner of their use. It also might have implications for the potential efficacy of depot preparations.

METHODS

The methods employed in our work have been extensively described at previous meetings of this organization and will again be described in a paper to be presented later in the session. In essence, heroin administration under blocked conditions was observed on a research ward for ten days. The narcotic blocking drug was administered (1) under nonblind conditions when all subjects experienced narcotic blockade after a period of ten days of unblocked heroin administration on the same ward, (2) under nonblind conditions where subjects did not experience unblocked heroin prior to naltrexone blockade, and (3) under double-blind conditions of administration where subjects received either naltrexone or naltrexone placebo. In the latter condition, blocked subjects were present on the research ward at the same time as unblocked subjects receiving heroin. In the latter design, the combination of patients on the ward at any time could include a heterogeneous sample (one, two, or three patients on naltrexone, with three, two, or one patient on placebo) or a homogeneous sample (all patients on naltrexone).

Data will be reported on 31 subjects who experienced narcotic blockade on the unit and and were offered naltrexone at follow-up.* These vatients had a mean of 7.6 years of heroin use (range 4-20) for which treatment was attempted a mean of 5.5 times in the

**Aftercare data will be reported on all patients who have been admitted to the unit. (see below)*

past (range 2-25).

Informed consent procedures have been described extensively elsewhere and are appended at the end of this report.

Narcotic Blockade: For all but two patients, narcotic blockade was produced by the daily oral administration of 50 or 75 mg naltrexone. During double-blind studies, an equivalent volume of placebo syrup was administered. In the initial study, involving two patients under blocked conditions, blockade was achieved by administering naloxone 500 mg four times per day.

Naltrexone was given at follow-up at the patients' local pharmacies. In the past 14 months, naltrexone consumption at the pharmacy was consequated by the payment of $1 to the patient after he took his daily dose. For each consecutive seven days of naltrexone consumption, $5 was banked at the hospital to be collected by the patient when he came for his monthly physical.

All patients were supervised by nursing staff thirty minutes after ingesting the narcotic blocking drug in order to assure that the medication was consumed and not regurgitated. Outpatient naltrexone consumption was super vised by the pharmacist.

Heroin Administration: Heroin was administered intravenously under medical supervision, and subjects always had the option of not taking heroin during the period of availability. The heroin administration schedule permitted patients to consume up to 6 me on Day 1 and 60 mg on Day 10 with an increase of 6 mg per day between Days 1 and 10. The permissible two-hour dose increased from 0.5 mg on Day 1 to 5 mg on Day 10; by waiting four hours between doses the subject could double his two-hour dose; by waiting six hours the subject could triple his dose. After six hours no further accumulation was permitted. Patients "worked" for heroin on an operant device: they accumulated points for which they were given a receipt every two hours. The points could be exchanged for heroin of specified potency.

Mood and Craving Assessments: In addition to utilizing heroin administration as an operant, subjects reported their desire for heroin on a craving scale which was a 100 mm line on which the subjects were asked to record their "craving for heroin" (from most to least). Subjects recorded their craving scores daily throughout the study and before and after each heroin administration. As reported elsewhere, craving scores correlated very strongly with actual heroin self-administration behavior under blocked and nonblocked conditions. Pulse, blood pressure, respiratory rate, and temperature were recorded daily (at 8 a.m.) and before and after heroin administration. Pupil diameter was recorded before and after the first administration of the day. An Osgood Semantic Differential Mood Self-Report was administered to the patients daily (at 8 a.m.) and before and after each heroin injection.

The Relationship Between Blocked Heroin Consumption and Demographic and Experimental Variables: Actual heroin consumption under blocked conditions was studied as a function of demographic and experimental factors. The total number and frequency of administrations and the total amount of heroin actually-consumed under blocked conditions served as the operant and the principal dependent variable in this analysis. The ages, years of heroin use, age at which use began, number of treatment episodes, and number of months in jail since beginning heroin were the demographic variables which were utilized to determine the effect of age, duration of addiction, and duration of presumably drug-free periods upon heroin self-administration behavior observed on the research ward. The ward conditions which were systematically studied included: blind or nonblind administration of naltrexone, experience of narcotic blockade with or without prior experience of unblocked heroin administration on the research ward, number of subjects per study, and homogeneous versus heterogeneous sample.

Followup Data: Because of the postulated relationship between "extinction of the operant response" and long-term outcome in the community utilizing a narcotic antagonist, data were also assessed relative to the outcome of patients who had experienced narcotic blockade on the research ward in terms of their outcome in the community (in particular, attempting to relate outcome in the community to frequency of heroin administration under blocked conditions). We have also compared the outcome of patients who only experienced unblocked heroin administration on the unit with those who experienced blockade in terms of community follow-up on naltrexone. We have also compared initial and longer-term outcome in the community for patients in nonblind and double-blind studies in which consumption of naltrexone in the community after discharge was and was not consequated with a monetary reward of $1 per day.

Finally, data will be discussed in relationship to data gathered in animal self-administration studies carried out in conjunction with Dr. Joseph Cochin and

TABLE 1

HEROIN SELF-ADMINISTRATION UNDER DIFFERENT STUDY CONDITIONS

		NONBLIND CONDITIONS (Designs 1 & 2)	DOUBLE-BLIND CONDITIONS (Design 3)	
		Homogeneous Sample	Homogeneous Sample	Heterogeneous Sample
BLOCKED HEROIN ADMINISTRATION	S's experience Unblocked Heroin on Ward Before Antagonist Blockade	Total n = 6 Design #1 only Mean # of Doses: 4.20 Mean Total Dose: 33.20 mg		
	S's Did not Experience Unblocked Heroin on Ward Before Antagonist Blockade	Total n = 3 Design #1 n = 1 Design #2 n = 2 Mean # of Doses: 21.22 Mean Total Dose: 327.00 mg	Total n = 5 Mean # of Doses: 5.40 Mean Total Dose: 27.40	Total n = 17 Mean # of Doses: 11.47 Mean Total Dose: 131.24

Mr. Gilbert Carnathan at Boston University, Department of Pharmacology.

RESULTS

Table I describes the experimental conditions that emerged from the nonblind and double-blind study designs. The total amount of heroin and number of self-administrations under each of these conditions are compared. The frequency of heroin administration under blocked conditions was positively correlated with the reported years of heroin use (Spearman $r = 0.45$, $p = < .01$) and negatively correlated with age of onset of heroin use ($r = -0.33$, $p < .05$) (i.e., those who started heroin at an earlier age challenged with greater frequency). Other demographic variables (number of months in prison and number of previous treatment episodes) did not show any relationship to frequency of administration under blocked conditions on the ward. Multiple Mann-Whitney U tests were employed initially to examine the effects of group size, homogeneity of sample, and nonblind versus double-blind conditions upon frequency of heroin self-administration in the presence of a narcotic antagonist. None of these factors served to differentiate rates of heroin self-administration under blocked conditions. Indeed, subjects with longer addiction histories (7-20 years) used more heroin under blocked conditions when compared with individuals with shorter addiction histories (4-6 years) in the same designs. Figures 1, 2, and 3 describe the heroin self-administration patterns of three subjects with shorter histories of addiction, while Figures 4, 5, and 6 describe these patterns in three more experienced users.

Within the double-blind design, some patients experienced narcotic blockade in a group with no unblocked subjects on the unit, while other subjects experienced blockade in the presence of subjects who were "getting high." Thus far, three subjects have separately experienced narcotic blockade in the presence of more numerous peers who were "getting high" self-administering heroin while on placebo naltrexone. Table II describes the outcome data. The differences between groups were not statistically significant because of the samll size of the sample. In addition, two out of three blocked subjects in the majority placebo condition (i.e., isolated antagonist administration) had used heroin for more than seven years. However, after adjusting for the effect of years of heroin use, the data still indicated a trend suggesting that heroin administration under blocked conditions (in an individual subject) may be more frequent where the demand conditions of the environment are consistent with an overwhelming stimulus of heroin availability (e.g., three subjects getting high while one subject is blocked).

Relationship Between Blockade on the Ward and Naltrexone Consumption in the Community: Finally, we examined the relationship between heroin administration under blocked conditions on the research ward and motivation to consume naltrexone in the community at least one day after discharge. There was no relationship between antagonist consumption in the community and frequency of administration under blocked conditions on the research ward. There was also no statistical difference in outcome between those who consumed placebo on the ward (and got "high" on heroin) compared with those who experienced narcotic blockade in the research setting. Thus, the participation of the patients in a program of narcotic challenges in the presence of other individuals who were getting high on heroin appeared to have no effect upon later naltrexone consumption in the community.

Over a three-year period of time, 83 patients have been admitted to the four-bed research ward for these studies,* of whom 49 completed the research ward experience and were eligible for treatment with naltrexone in the community. Of the 49 who were eligible for outpatient treatment, 40 actually consumed naltrexone in the community. In the nondouble-blind studies (Group 1), 21 subjects were admitted and ten were eligible for naltrexone consumption in the community;** in the double blind studies prior to monetary consequation of naltrexone consumption in the community (Group 2)) 30 patients were admitted and 15 were eligible for naltrexone consumption; while in the double-blind studies after we initiated monetary consequation of naltrexone consumption in the community (Group 3), 32 patients were admitted and 23 were eligible for naltrexone consumption in the community. (Table III) All ten subjects in Group 1 actually con-

Eight additional subjects have been admitted for acute studies and two patients were put on naltrexone as outpatients because they were not deemed eligible for the inpatient studies.

**Only six patients in this group completed the 60 days during a single admission; two patients were readmitted after discharge for misbehavior and were allowed to complete the study on the second admission; one patient was admitted for blockade only and one patient signed out AMA after receiving naltrexone and refusing to stay on the ward during the 10 days of experimental blockade.*

TABLE 2

BLOCKED HEROIN ADMINISTRATION IN DOUBLE-BLIND STUDIES

	HOMOGENEOUS SAMPLE	HETEROGENEOUS SAMPLES		
	All Antagonist	Majority Antagonist	Equal Number	Majority Placebo
	N = 5	N = 9	N= 5	N = 3
Mean	# of administrations 5.400	10.33	9.4	18.33
Mean	Total Dose 27.400mg	120.89mg	96.60mg	220.00mg

Doses F = 1.663, p < .211
Total Dose Consumed F = 1.245, p < .323

sumed naltrexone in the community while five out of 15 and 19 out of 23 in the remaining groups actually consumed naltrexone in the community. Chi-square determination indicated a statistically significant difference in actual naltrexone consumption between subjects in Groups 1 and 3 compared with Group 2. Multiple T-tests were performed to compare longer-term naltrexone consumption in patients from the three groups who actually began naltrexone consumption in the community. Median naltrexone consumption at one month, three months, and six months in the three groups was compared. There was a trend for patients in Group 1 ($p = <0.1$) to consume naltrexone longer in the community than patients in Groups 2 and 3. There were no differences in the three groups relative to six months consumption of naltrexone. Of the ten patients who have remained on naltrexone for more than 90 days, seven relapsed to opioid use after stopping naltrexone, two have remained drug free, and one is continuing on naltrexone and in individual counseling. Both patients who have continued drug free after stopping naltrexone had changed the location of their residence and had found stable employment. All but one of the seven patients who relapsed after stopping naltrexone were unemployed at the time of relapse. Six patients consumed naltrexone in the community from 60 to 90 days; all but one relapsed to opioid use. The single exception was steadily employed at the time that he discontinued naltrexone. One of those who relapsed was working at the time of this relapse and another patient who relapsed ultimately moved out of state as a fugitive from justice. We have no follow-up data on him subsequent to his departure. Six patients consumed naltrexone from 30 to 60 days and four of the six relapsed subsequent to stopping naltrexone. Two of the patients are currently in treatment. Eighteen patients consumed naltrexone from 0 to 30 days (as of April 30); three of the patients are continuing naltrexone consumption as part of their overall treatment program. The remainder relapsed to opioid use. Relapse for many of our patients was not marked by an inevitably bad outcome since a number of patients followed their relapse with reentry into treatment with methadone maintenance, self-help groups, and, in some cases, naltrexone.

Relation Between Background Data, Experimental Conditions, and Outcome: Demographic variables from the TCU (Texas Christian University, Institute of Behavioral Research, Narcotic Addict Reporting Program Admission Record) forms filled out on all patients on admission were coded and factor analyzed. Using the Varimax solution of orthogonal rotation, factor scales were obtained by taking the average of those items which had loadings of 0.40 or higher on a given factor after all items had been converted to standardized T-scores. Seven factor scales were obtained. Three distinct outcomes were compared: patients who were eligible but failed to consume naltrexone; patients who took naltrexone for 1-30 days; and patients who consumed naltrexone for more than 30 days. A two-way analysis of variance compared patients in the three groups relative to the seven factors. Two of the factors had relevance to outcome on naltrexone. Patients who were arrested at a younger age, started heroin

FIGURE 1

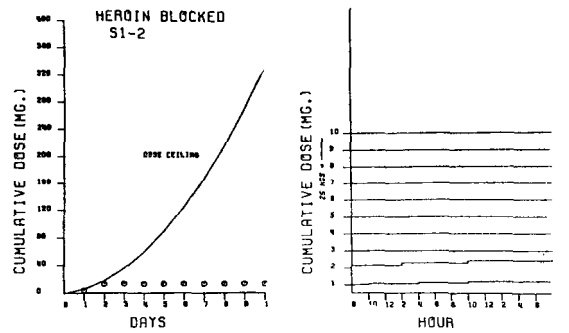


FIGURE 2

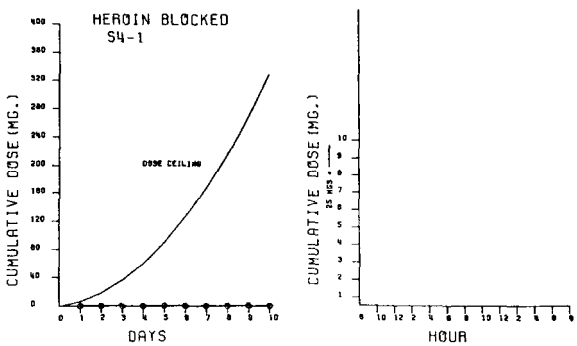
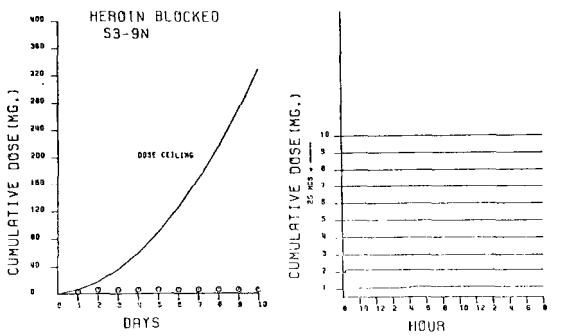


FIGURE 3



at a younger age, participated in more treatment programs, and were not raised by two parents through age 12, tended to do poorly ($F = 4.59$, $p < .015$). In addition, patients whose mothers ($F = 1.631$, $p < .210$) and fathers ($F = 1.776$, $p < .184$) had the least education tended to do best in terms of actual naltrexone consumption. Multiple chi-square analyses with each of the demographic variables treated individually confirmed these relationships. In aadition, those patients living with spouse, parents or relative on admission did better than those patients living with friends, living alone, or with no stable arrangement. (Chi-square = 13.583, $p < .194$) Patients participating in the double-blind studies where naltrexone consumption in the community was not consequated (by $1/day) did significantly more poorly than patients who participated in the nonblind studies or patients who participated in double-blind studies where naltrexone consumption in the community was consequated (chi-square = 21.592, $p < .002$).

Anecdotally, we can report that opioid challenges to narcotic blockade in the community were rare. When patients did choose to challenge, they generally did so when they thought that the narcotic blocking drug had cleared. Alternatively, patients have reported that they have encountered former associates and pushers in their neighborhood and used the presence of naltrexone to reinforce their determination to remain opioid free.

DISCUSSION

Heroin self-administration (under blocked or unblocked conditions) in an experienced addict is a complex operant which we have defined in terms of the frequency and total dose of heroin self-administration over a ten-day period. Naltrexone self-administration in the community is also a complex operant which, based upon our data, appears to be more likely to occur in our program among patients with certain demographic characteristics and in patients who may have differed in "motivation" to consume naltrexone at the start of the outpatient period. Those individuals who participated in nonblind naltrexone administration on the ward (Group 1 patients) were motivated to remain on the inpatient unit for nonblind naltrexone administration. Patients who participated in the double-blind studies were prepared to remain on the ward for a shorter period of time and took naltrexone under conditions when they expected that they may or may not receive naltrexone during the period of heroin availability. Thus,

it was our impression that the research design in the first group of patients may have screened out the "less motivated" individuals prior to discharge. This impression seems to have been borne out since all ten patients who received naltrexone on the ward actually consumed the drug in the community at follow-up. In contrast, only five of 15 patients in the second group actually consumed naltrexone in the community. When we contingently reinforced naltrexone consumption in the community, 19 of 23 graduates of the double-blind study actually consumed naltrexone in thecommunity. Thus, to some extent, contingent reinforcement of naltrexone consumption in the community may have overcome the diminished screening function of the inpatient double-blind studies. Nevertheless, "more motivated" patients from the first study designs did tend to consume naltrexone for a greater number of visits over the course of the first three months in the community.

The best predictors of outcome were related to demographic variables and some experimental conditions, but not to the experience of blocked heroin on the ward. Long-term outcome was related best to stable employment, but the sample has been too small at this time to draw definitive conclusions. Heroin consumption under blocked conditions on the ward did appear to anticipate outcome in the community in the following respect: naltrexone consumption serves as a discriminative stimulus (S^{Δ}) for heroin being unavailable to the patiet. The power of a cognitive label relative to the power of a conditioned stimulus has been described by Wikler in a study of five "post addicts" who received subcutaneous injections of nalorphine or normal saline in lieu of regularly scheduled doses of morphine or methadone at irregular intervals and on different days. Saline injections rapidly ceased to invoke a conditioned response once it was clear that the subjects "had been watching each other and if the first one to receive an injection did not get 'sick' within two to three minutes they all concluded that the 'shot was a blank' and reacted accordingly."(2) Cognitive function served to alter the stimulus properties of the experiment such that saline injections ceased to elicit the withdrawal syndrome.

In previous reports, we have pointed out the relationship between self-reported assessments of craving and the presence of heroin on the research ward.(10) These data are remarkably consistent with data reported by Ludwig (14) relative to subjective reports of craving in alcoholics in response to the "alcohol stimulus." In our studies, craving scores remain elevated under blockade so

FIGURE 4

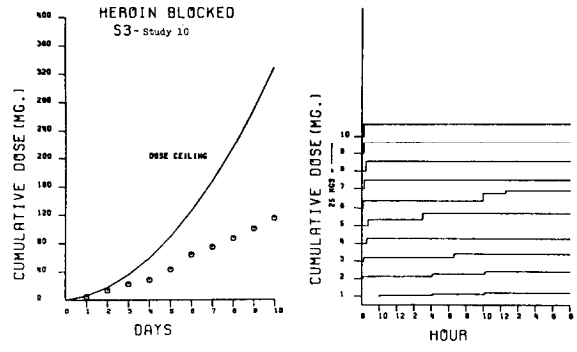


FIGURE 5

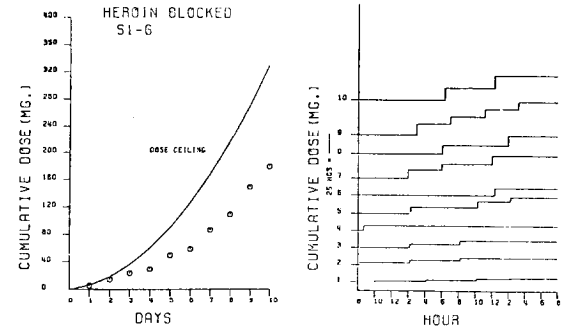


FIGURE 6

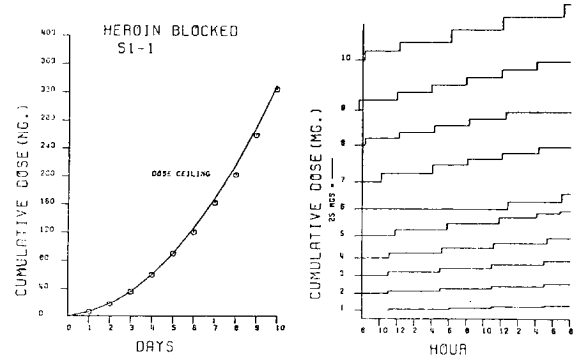


TABLE 3

AMBULATORY NALTREXONE CONSUMPTION IN ALL PATIENTS ADMITTED TO THE RESEARCH UNIT

	Group 1 Nonblind studies	Group 2 Double-blind studies prior to consequation of ambulatory naltrexone consumption	Group 3 Double-blind studies after consequation of ambulatory naltrexone consumption
Admitted	21	30	32
Eligible for Naltrexone	10	15	23
Consumed Naltrexone in the Community	10	5	19

long as heroin self-administration continues. Once the patient concludes that he is not going to get high, he ceases to self-administer heroin. In reports of his work, O'Brien (15) has observed that patients begin to find Dilaudid self-administration to be an aversive experience over time, ostensibly because the stimulus conditions have changed and the environment no longer signals opioid availability. Under these conditions, opioid self-injection apparently becomes aversive. The data are also consistent with the outpatient data gathered by Kleber and colleagues in New Haven (16) which indicate that patients on cyclazocine only rarely challenged blockade.

The inpatient data gathered by us suggest that patients continue to self-administer heroin under blocked conditions so long as they anticipate that heroin may be "available." When they learn that heroin is unavailable (i.e., that they are on naltrexone), their craving for heroin falls dramatically and they stop heroin challenges. It is possible that when unemployed outpatients in familiar drug-using environments stop using naltrexone (even after six months), the stimulus properties of their environment (interoceptive and exteroceptive) again suggest the availability of heroin.

Some have argued that active extinction procedures are not necessary to effect extinction (17) since patients will extinguish classically conditioned responses in the presence of the conditioned stimuli previously associated with abstinence phenomena. At a previous meeting of this group O'Brien and his co-workers presented data that suggested that patients who had been through his forced extinction paradigm did not manifest autonomic changes in response to slides of heroin self-administration behavior. (15) In contrast, patients who had merely been detoxified or who were being maintained on methadone maintenance did evince such autonomic responses in response to such slides. Our human data do not permit an assessment of whether classically conditioned abstinence was extinguished in the presence of naltrexone. They merely suggest that active extinction does not appear to take place in the presence of naltrexone. As Wikler has stated,

> Mere withdrawal of opioids and prolonged retention of the patient in a drug-free environment does not extinguish the conditioned responses any more than satiating a rat with food and keeping it away from a Skinner box for a period of time will 'cure' it of its lever-pressing 'habit,' previously reinforced by food rewards under conditions of food deprivation. By analogy with extinction procedures known to be effective in the laboratory,

> post-detoxification treatment programs should include procedures for active extinction of both 'conditioned abstinence' and pharmacologically reinforced opioid-seeking behavior, namely: repeated elicitation of conditioned abstinence without the possibility of reinforcing this conditioned response by reestablishment of unconditioned physical dependence; and frequent repetition of the addict self-injection ritual under conditions that preclude suppression of opioid abstinence phenomena conditioned or unconditioned.(2)

The mere presence of other addicts getting high over a ten-day period on our research ward did not result in persistent heroin self-administration under blocked conditions, although persons experiencing blockade as individuals in the presence of three subjects getting high tended to maintain heroin self-administration behavior for a longer oeriod of time. Frequency of self-administration under blocked conditions appeared to correlate best with number of years of prior heroin use, data remarkably consistent with laboratory rodent self-administration studies we will be reporting at these meetings.(18) The persistence of this behavior during naloxone blockade is consistent with the findings of Goldberg, Woods, and Schuster that stimuli repeatedly paired with intravenous self-injections of morphine during self-maintained dependence will persist for prolonged periods of time.(8) In contrast, classically conditioned responses were extinguished rapidly in other studies. (7) The questions that we have raised about the extinction paradigm in antagonist treatment should not lead to conclusions about the eventual efficacy of these drugs. They may suggest ways of incorporating specific psychotherapeutic, behavioral, and social interventions in a total treatment program.

In an excellent review article by Ludwig (14), the author suggests that "a wide range of… interoceptive cues (e.g., produced by apprehension, loneliness, viral infections, etc.) ...could be capable of evoking the experience of craving and thus be capable of increasing the predisposition to drink" in alcoholic patients. In the conditions of our research ward, the discovery by our patients that they were on naltrexone in the double-blind study (or the period of naltrexone administration in the nonblind studies) was associated with a diminution in anxiety, tension, and depression. It is our impression that the cognitive labeling process is of great importance in the successful treatment of the narcotics user with naltrexone. During conditions when the stimulus properties of the environment (interoceptive and exteroceptive) suggest the availability of heroin, patients experience a dysphoric response that may not only be marked by classically conditioned abstinence, but also by anxiety and tension associated with an approach-avoidance conflict associated with the euphoric high generated by previous opioid administrations, as well as previous encounters with the aversive consequences of drug use. In this circumstance, tension escalates and relief can be obtained by the administration of an opioid. The dysphoria is labelled "craving" and is associated with a feeling of inevitability. Conditioned abstinence phenomena may only be one part of the symptom picture, but we suspect that the ambivalence in the conflict may be more central to the relapsing phenomenon as it manifests in human beings. Naltrexone consumption is a conscious act by the patient to enter a drug-free setting for a period of 24-48 hours. It is marked by tension reduction because in the circumstances the stimuli associated with heroin availability (including classically conditioned abstinence) are not present. It is probably not surprising that our success rates with naltrexone are analogous to the success rates of Antabuse in the treatment of alcoholism. While alcohol consumption on Antabuse does have aversive consequences, both Antabuse in the alcoholic and naltrexone in the narcotics user involve a conscious decision by the patient to avoid interoceptive and exteroceptive stimuli that are associated with the availability of the drug of abuse. It is possible that we would have seen more insistent heroin challenges under conditions of precipitated narcotic withdrawal or under conditions where naltrexone and placebo administration were carried out in a random, double-blind, cross-over design (i.e., the prolongation of uncertainty re: heroin availability). Since the drug is not normally used therapeutically in either of these situations, the design that we have actually employed may have greater significance so far as treatment applications are concerned. Our data suggest that contingent reinforcement of naltrexone consumption may offer some short-term advantages relative to the initiation of naltrexone consumption by the patient in the community. Motivation to continue naltrexone consumption, however, appears to be a function of the availability of alternative reinforcers (e.g., job; meaningful, affectional relationships, etc.). We would urge that programs utilizing naltrexone consider these needs in developing their treatment programs. It is our impression

that depot preparations will be seen by patients as a "sentence" to a drug-free setting and that extinction will no more take place under conditions of depot administration than under conditions which we have observed. Moreover, our data on patients who have been on naltrexone for six months suggest that, even the patient on long-term antagonist treatment must eventually confront the time when he is naltrexone free and opioids are again "available."

INFORMED CONSENT PROCEDURES

The informed consent of heroin addicts for a research program that at some time involves the administration of heroin is an issue to be carefully considered and reviewed. In addition to the usual human studies committee reviews, this project was also scrutinized by a group of citizens from the Governor's Drug Abuse Prevention Planning Council in Massachusetts and staff persons from the Departments of mental health and public health in this state. At the federal level, separate committees of the Food and Drug Administration and the National Institute of Mental Health reviewed the procedures in terms of the ethical and humane considerations and the likely benefits and risks to the subject.

All persons were recruited by referral from drug rehabilitation facilities in Massachusetts or by former patients. Prior to acceptance in our program, each individual was evaluated medically and psychiatrically. Admission to another facility for inpatient or outpatient detoxification prior to admission to the research facility was recommended to all patients. Verbal descriptions of the project were supplemented by an eight- to ten-page patient handbook, which was given to the patient prior to admission. He was also taken on a tour of the research ward and McLean Hospital, and was given the opportunity to talk with former patients.

On the day of admission, he was interviewed by an attorney (a member of the hospital Human Studies Committee), who, after being satisfied that the patient was well informed and understood fully the nature of the proiect. obtained the individual's signature on the informed consent form. No patient was accepted by referral from the criminal justice system, and all patients were volunteers who were free to leave the project at any time. Each could receive up to $700 for participation in the program. If a patient did drop out, he was permitted to keep money already earned during his stay.

ACKNOWLEDGMENTS

This research was supported by NIMH Grant #5 P01 DA 00257: Harvard-Boston University Center for Biobehavioral Studies in the Addictions: NIMH Contract #HSM 42-72-208: A Research Paradigm for the Study of Opiate Antagonists, McLean Hospital, Belmont, Massachusetts (Expired December 31. 1974) and SAODAP Grant #DA 4 RG 010: Clinical' Research Center, McLean Hospital, Belmont, Massachusetts, 02178.

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NALTREXONE IN A BEHAVIORAL TREATMENT PROGRAM

Charles O'Brien, M.D., Ph.D.
Robert Greenstein, M.D.

Arguments favoring narcotic antagonist treatment usually emphasize the conditioning factors in addiction. Wikler's pioneering clinical observations (Wikler, 1948) and experimental work stimulated much thought and effort in this area. Now that a drug is available which seems to satisfy many of the criteria for a clinically useful narcotic antagonist, how are we progressing in the application of these theoretical principles? In order to address this question, we must first examine some of the conditioning factors in human narcotic addiction. Animal studies have been invaluable in the development of this area (for an excellent review, see Wikler, 1973), but cognitive factors make direct extrapolation to the clinical situation very difficult.

CONDITIONED ABSTINENCE

When a detoxified addict reports the onset of withdrawal symptoms on return to his drug-using environment, we my wonder whether he is attempting to rationalize his relapse or perhaps he is reporting protracted abstinence (Martin, 1972). Patients may report these symptoms after return from months or years in a prison or therapeutic community. There is now clinical evidence that these symptoms occur naturally in patients receiving methadone maintenance (Whitehead, 1974; O'Brien, 1975b) and experimental evidence that they can be produced in a laboratorv (O'Brien, 1975a). After a classical conditioning procedure, a previously neutral stimulus was able to elicit yawning, tearing, lacrimation, and changes in heart rate, respiration, blood pressure, and skin temperature. These changes showed evidence of extinction after repeated unreinforced trials.

The changes may, of course, be more subtle. Teasdale (1973) reported evidence of tension when addicts were shown slides of drug-related materials. Meyer (1976) reported increased craving scores when addicts on a research ward were in a "drug available" situation. Our group has noted increased craving and decreased skin temperature (a sign of withdrawal) in detoxified addicts going through "cooking-up" rituals in preparation for self-injection.

Since the data now support the clinical reports, we can assume that at least some detoxified addicts develop conditioned abstinence symptoms, although we have little information as to which situations are the most provocative. Naltrexone may be helpful by allowing the patient to be exposed to these stimuli while in the cognitive set of the "no drug available situation." Of course, the strength of the conditioned responses may be reduced by this cognitive set just as Meyer's (1976) patients reported reduced craving when they knew heroin was not available. This factor would prolong the time required for extinction of these responses, and would raise the possibility that they would reappear when the patient stops naltrexone, i.e., the cognitive set is different.

NEEDLE RITUAL CONDITIONING

A second type of conditioning is related to the "needle freak" phenomenon (Levine, 1974). This has been observed occasionally by clinicians and refers to the effects produced by the ritual of injection itself rather than to the pharmacological effects of the drug injected. The potency of street heroin is notoriously variable and some bags contain little or no measurable heroin. Among applicants for methadone treatment, 10-20s have multiple fresh needle marks but negative naloxone tests for physical dependence (Blachly, 1973; O'Brien, 1975b). Stimuli which have reliably preceded drug effects may exert effects themselves when they occur in the absence of the drug. These stimuli may include the environment of the shooting gallery, the smell of the "cooker," the act of "tying off" and flushing the syringe with blood, and the internal effects of the adulterants (e.g. quinine). The conditioned effects theoretically might be opposite to the narcotic agonist effects. This would be counteradaptive effects of Wikler (1973) or the opponent process as proposed by Solomon (1974). Siegel (1975) has experimental evidence in rats supporting the counteradaptive effects and perhaps explaining part of the phenomenon of tolerance. Our own work with humans has thus far not detected counteradaptive effects in addicts after saline injection or blocked narcotic injections. Patients show withdrawal phenomena (craving, decreased skin temperature) during pre-injection rituals, but after injection they report mildly pleasant effects (taste, some rush, occasionally some high) when saline or narcotic in the presence of naltrexone is injected (O'Brien, 1975b).

The influence of cognitive set is an important consideration when dealing with humans. In order to study what might occur in the natural situation, the test situation must be as realistic as ethically possible. When the subject expects to feel no effect from an injection, he usually reports no effect. We have some data on individual patients which indicates that even objectively recorded autonomic changes may be influenced by cognitive expectations.

Our group has been trying to determine whether patients on naltrexone are benefited by techniques which extinguish the effects of these rituals. We have permitted addicts to self-inject narcotics or saline in the laboratory under naturalistic conditions. In our pilot work (O'Brien, 1974) we showed that the first few injections of either hydromorphone (1 to 4 mg) or saline are interpreted as pleasurable, although pupillary changes are minimal. These pleasurable effects in the presence of an antagonist (either cyclazocine or naltrexone) are rapidly extinguished, however, and subsequent injections become neutral or annoying. We are currently conducting a study of the effects of this procedure as compared to naltrexone and only traditional counseling. Patients are assigned to either extinction trials or a control group. Our initial follow-up (6 months post treatment) shows a slight (not significant) increase in proportion remaining opiate-free for those who participated in the trials. A major difficulty with the study is that patients become so annoyed by the procedure that they usually refuse to participate in more than a few trials (5 to 10). Those who take more trials (up to 45) tended to do better, but the numbers are too few to be conclusive. One consistent finding was that those who remained on naltrexone longer tended to do better whether or not they participated in self-injection.

ACTIVE VS. “PASSIVE” EXTINCTION

The finding that duration on naltrexone seems to predict outcome at follow-up suggests the possibility that efforts at self-injection may be unnecessary. The patients in our control group, however, cannot be considered to be undergoing "passive" extinction. Passive extinction implies lack of active control by the subject. This would apply to an animal kept in a cage apart from the previously-conditioned situation or to a human addict kept in prison away from the drug environment. Extinction in these cases does not occur, although there may be considerable decay in strength of responses depending on the duration of conditioning and duration of separation from the test stimuli.

Our control group underwent active extinction because they maintained control over their access to drug-related stimuli. Some of them tested the naltrexone with a "street fix" and some did not. We do not yet know whether spontaneous voluntary testing has any effect on outcome, but we intend to investigate this variable. The control group did not go through self-injection rituals in the laboratory, but they did expose themselves to many of the other stimuli which had formerly preceded drug effects. It may either be unnecessary or provide only minimal advantages to expose the patient to all drug-related stimuli up to and including the act of injection. The question is not whether extinction should be active or passive, but how far down the chain of drug-related stimuli need we systematically extinguish? Also, need we apply principles of systematic extinction? Perhaps as Meyer (1976) suggests, we should focus on the contingencies which increase the probability of long-term naltrexone ingestion among out-patients and let extinction take care of itself. These questions have not yet been answered.

HOW COMPLETE IS THE NALTREXONE BLOCK?

Our work with self-injection has given us the opportunity to assess the completeness of antagonist blockade under double-blind conditions. The results show that while naltrexone at 120 mg markedly reduces narcotic effects up to 48 hours, some effects remain. Table I summarizes some of our previously published data (O'Brien, 1975c) on 82 trials, 48 hours after 120 to 200 mg naltrexone. We have similar data for 24 hours and 72 hours and for higher naltrexone doses. The hydromorphone trials even at 1 or 2 mg showed on the average greater effects as measured by patient, observer, and pupillometry than saline trials. Only 17% of the 3-4 mg hydromorphone trials were rated as no effect whereas 97% of the saline trials were rated this way. Ratings of rush, high, and pupil constriction all followed this dose-response trend. These effects, of course, were slight and might well be missed in a single-blind or nurse injection study. There is also the possibility that hydromorphone has a greater affinity than morphine for opiate receptors and thus would show effects in the presence of naltrexone while heroin would not. More importantly, the effects were not sufficiently rewarding to induce the subjects to continue self-injection. We have not found a significant decrease in these effects over time on naltrexone, but it is possible that they may be reduced as active naltrexone metabolites accumulate with repeated doses.

IS NALTREXONE CLINICALLY EFFECTIVE?

There seems to be no doubt that naltrexone is effective as an antagonist of narcotic effects and so far it seems to be reasonably safe. But are patients helped by our present methods of administering the drug? 'Those of us who have used the drug in fairly large numbers of patients can all cite examples of patients who did well on naltrexone and even some patients who remained drug free for extended periods after stopping naltrexone. Our own six month follow-up data is presented elsewhere in this symposium. So far, however, no one has shown that the remission rate for patients on naltrexone exceeds spontaneous remissions in similar untreated patients. Further there have been no controlled comparisons with other treatments for narcotic addiction. Of course, no other addiction treatment meets these criteria either. Such studies are difficult, but not impossible to perform. Perhaps the comparison should be with another drug-free approach such as therapeutic community, rather than a maintenance approach. Here, just as with naltrexone, there is a high attrition rate and a high relapse rate after treatment is stopped. In fact, it is our impression that therapeutic community graduates can benefit from a period on naltrexone after returning to the community, but we have been unable to get sufficient numbers for an adequate trial. Most of our efforts at follow-up are contaminated because our patients have received multiple kinds of treatments and it is misleading to attribute outcome to the one you happen to be studying. The life table approach seems to hold promise in sorting this out. As far as the conditioning aspects are concerned, a wide variety of autonomic conditioned responses have been found which are available for extinction. This is only part of the illness, however. We have not solved the problem of cognitive set and we certainly cannot work in isolation from the complex social factors such as education, employment and poverty which may be much more potent than treatment variables.

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TABLE 1

Effects of double-blind challenge injections 48 hours after taking 120-200 mg of naltrexone

	placebo	hydromorphone dose	
	0	1 or 2 mg	3 or 4 mg
Number of trials run	30	28	24
I. "High" and "Rush"	0 (0%)	1 (4%)	3 (12%)
Mean pupil constriction (mm)*	-	.25	.25
"Rush" (patient rating; 0-3)	-	1.0	2.0
"Effect" (observer rating; 0-5)	-	2.0	2.7
II. "Rush" only	1 (3%)	9 (32%)	17 (71%)
Mean pupil constriction (mm)*	.00	.30	.38
"Rush"	1.0	1.0	1.1
"Effect"	1.0	1.0	1.5
III. No effect**	29 (97%)	18 (64%)	4 (17%)
Mean pupil constriction (mm)	.04	.16	.31

* This is actual change (un-magnified) under low light, non-flash conditions.

** On five of these (four at 1-2 mg Dilaudid; one at 3-4 mg) the observer rated a "slight" or "questionable" effect. No effect was reported by the patients.

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CLINICAL EXPERIENCE WITH NALTREXONE IN A BEHAVIORAL RESEARCH STUDY: AN INTERIM REPORT

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INTRODUCTION

Early studies of naltrexone showed that it was a potent antagonist of narcotics with minimal agonistic properties (Martin 1973). There were indications that naltrexone was potentially an ideal antagonist for clinical use. It was apparently safe, nonaddicting and relatively-long-acting. A single 50-mg oral dose blocked the effect of 25 mg of heroin for up to 24 hours, and large doses provided "protection" for 48 to 72 hours (Resnick 1974). Wikler (1974) proposed that human subjects taking narcotic antagonists be encouraged to undergo a series of blocked, or unrewarded, opiate self-injections to produce extinction of drug using behavior. In practice, most patients stabilized on antagonists test the blockade once or twice and then stop because they feel they are wasting their money. O'Brien (1974, 1975) reported a pilot study in which patients treated with cyclazocine participated in a series of self-injections of hydromorphone or saline in a double-blind procedure. Subsequently we have tested similar procedures using naltrexone. Our initial experience with 54 naltrexone patients has been reported (O'Brien, 1975). The following is an update of the Naltrexone-Behavioral Research Project and includes the methodology of naltrexone stabilization and medical observations.

METHOD

1. Clinic setting and patient population:

The Drug Dependence Treatment Service (DDTS) of the Veterans Administration Hospital, Philadelphia treats drug dependent veterans in the southeastern Pennsylvania-New Jersey-Delaware region. 761 patients were seen at the clinic in 1975, with over 300 active each month. Subjects for the naltrexone project were recruited from the clinic and from three detoxification units in Philadelphia. Contact was maintained with methadone maintenance programs and therapeutic communities in the area, but a negligible number of people were referred by them. From October, 1973 through March, 1976, a total of thirty months, 264 patients expressing an interest in Naltrexone were

screened and evaluated. Of these, 142 successfully completed detoxification and took at least one dose of naltrexone. Thirty-one were treated two or more times for a total of 179 treatment episodes. The average age of patients treated was 26.9, with a range of 20 to 47 years. Fifty-nine percent were black, and 40% were white. One subject was Puerto Rican. Two women with hysterectomies were included in the treatment population. The average length of dependence on opiates was five and a half years, with a range of one to 24 years. Sixty-three patients (44%) were working or in school when they applied for treatment and 47 (33%) were married. Twenty-three percent were non-veterans. Fifty percent were addicted to street heroin when screened, 33.7% were in methadone maintenance treatment, and 16.5% were drug free because they recently completed detoxification or were released from prison. A large portion of the heroin addicted patients had been treated previously with methadone at the clinic and asked for naltrexone when they returned.

2. Intake and Screening:

During screening patients were evaluated by a staff psychiatrist, drug counselor, research nurse, and psychology technician. Physical examination, laboratory studies, including a CBC, SMA-12, serology, Australian antigen and urinalysis, EKG, and chest X-Ray were done routinely. A Brief Psychiatric Rating Scale, Wonderlic Personnel Test, Gordon Personal Profile, Beck Depression Inventory, and anxiety and symptom check lists were completed. Patients with active medical disorders such as gastric ulcer, hepatitis, or heart disease, and women with child bearing potential were not eligible for treatment.

3. Induction:

A Naltrexone-Behavior Research Fact Sheet was given to interested patients and questions concerning the program were answered by the staff. The consent form, including a description of the behavioral aspects of the program, was reviewed and signed after completion of detoxification. The naloxone test, a safe, reliable method for determining the presence of significant physical dependence on opiates (Blachly, 1973) was done prior to starting naltrexone. Thus, patients who still had significant physical dependence experienced precipitated withdrawal for 30 to 60 minutes following injection of naloxone, rather than the prolonged withdrawal of four to twelve hours which might follow an initial oral dose of naltrexone. A relatively large dose of naltrexone (0.4 - 0.8 mg) was administered intravenously in order to produce definitive results. In addition to subjective and observer ratings of the symptoms precipitated by naloxone, pupillometry using a polaroid reduced-flash technique was done on 50 subjects. Changes in the size of the pupil were an objective measure of naloxone effect. Pictures were taken at baseline and again ten minutes after naloxone injection.

Naltrexone Placebo was given for one to three days and the naloxone test was administered 48 to 120 hours after the last dose of opiate. If the test was negative (no response) or mildly positive (+1: a warm feeling in the stomach, a mild chill, slight irritability, and minimal or no pupillary dilation) 10 mg of naltrexone was given one to two hours after the test. If no withdrawal symptoms were observed within 2 hours, a second dose (25 to 50 mg) was given. If the naloxone test was moderately or strongly positive, patients were asked to wait another 24 to 48 hours before the test was repeated and naltrexone was given. Strongly positive (+2 to +4) responses consisted of pupillary dilatation, chills, anxiety, abdominal cramps, and diarrhea; these disappeared 40 - 60 minutes after the naloxone injection.

Most patients were inducted onto naltrexone in the hospital. Of the 179 treatment episodes 45 were started on an outpatient basis. Fifteen of these were done at the start of a second or third treatment episode. In outpatient Induction, a history of being opiate-free a minimum of 48 hours was required. Urine for drug screening was collected and a naloxone test was done. If the test was negative, patients were given a dose of naltrexone placebo. followed one hour later by 10 to 25 mg of naltrexone. If there were no withdrawal symptoms during the next hour, they were told they had a low level of protection against narcotics and were sent home. The next day they were given 25 or 50 mg of naltrexone, and the dose was then increased daily until the maintenance level was reached. All naltrexone in the study was dispensed in juice and no take-home doses were allowed.

4. Outpatient maintenance:

Patients were stabilized on 100 mg of naltrexone on Monday and Wednesday and 150 mg on Friday. During outpatient treatment, counselling sessions with a research nurse or drug counselor were scheduled one to three times per week. In addition, group therapy for naltrexone patients was conducted during one 13 month period.

5. Medical evaluation:

Physical examination, laboratory studies, and EKG's were repeated at two and four weeks, then monthly and at termination. Chest X-rays were done at three and six months of treatment,

and at termination. Vital signs were taken at each medication visit and symptom check lists were filled out by the research nurse once weekly. Patients with medical problems were evaluated by a staff physician and were referred to the appropriate specialists when indicated.

RESULTS

1. Induction:

Naloxone, used as described, usually produced minimal or no changes in recently detoxified addicts. Of 134 tests done 48 to 120 hours after the last dose of heroin or methadone, only 19 were strongly positive. Fourteen of these nineteen patients insisted on starting naltrexone within 24 hours of the naloxone responses because of their "need" to leave the hospital. All developed precipitated withdrawal again when a low dose of naltrexone was ingested. As a result of this experience, we no longer permit this option. All of the patients with minimal or no response to naltrexone were safely started on naltrexone with no symptoms or only mild precipitated withdrawal.

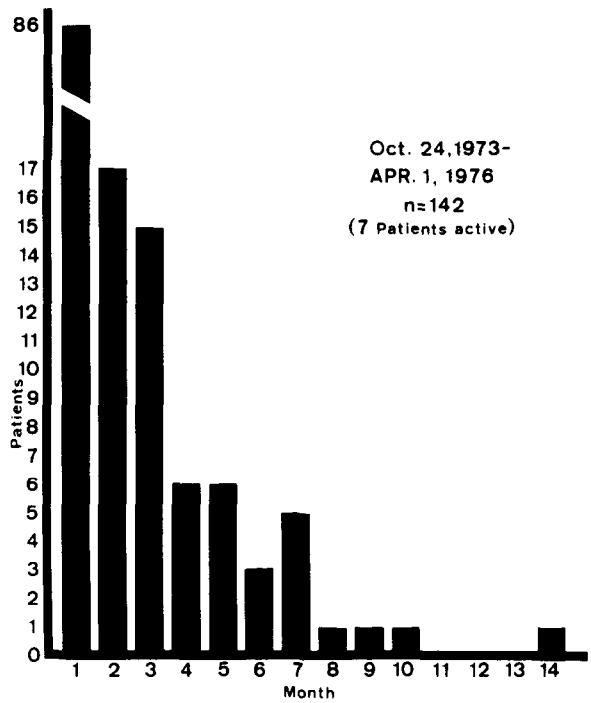
2. Early Dropouts:

Graph 1 shows the length of time in treatment for those patients who were given naltrexone. Of the 142 who began induction, 28 stopped naltrexone after one or two doses and another 30 stopped treatment during the first week. Half of the early dropouts complained of anxiety or abdominal cramps. The rest were asymptomatic but changed their mind about taking naltrexone. When they returned to the clinic after several days or weeks, they reported being unable to feel up to 25 bags of heroin when used up to 24 hours after taking naltrexone. Although all patients expressed firm motivation about giving up drugs when they asked to start on naltrexone, marked ambivalence was evident later. Several said they tried naltrexone because it was a new drug and they wanted to see whether it would make them high. Others wanted to see if it "really worked," and once they found that it did, they stopped it. Two patients worried that their ability to get high had been taken away permanently. Some with chronic anxiety or depression felt these symptoms were relieved by opiates and exacerbated by naltrexone. Almost all of the early dropouts requested methadone maintenance treatment.

3. Short and long term treatment:

Patients were arbitrarily divided into a short term group of 43 who attended for one to eight

GRAPH 1



LENGTH OF NALTREXONE TREATMENT

weeks and a long term group of 41 who took naltrexone for more than eight weeks. Tables I and II compare urine results for the two groups with methadone maintenance patients matched for time in treatment. Urines were analyzed by thin layer chromatography and were confirmed by radioimmuno assay and gas chromatography. Morphine could be detected for up to three days, quinine and amphetamines for a week, and barbiturates for four or five days after use. Several patterns of drug use were apparent from interviews and urine analysis. Some patients never tested naltrexone's blockade, and their urines were clean throughout treatment. Many used opiates early to determine if they were protected. Thereafter they did not use because they "didn't want to waste the money." Nine used amphetamines and four used barbiturates intermittently. Eleven patients with histories of regular alcoholic intake drank while taking naltrexone (Four of them also abused amphetamines). One was terminated because he came to the clinic drunk on three occasions and a second stopped because of epigastric distress. Another had elevated bilirubin during treatment (see medical findings). Graphs 2 and 3 give a more detailed analysis of the patterns of drug use in 52 patients. For each of the three treatment duration groups an index was calculated by dividing the number of weeks during

TABLE 1

COMPARISON OF URINE RESULTS FOR LONG-TERM (>8 WEEKS) NALTREXONE PATIENTS WITH A MATCHED GROUP OF METHADONE PATIENTS (NAL=30; METH=19)

	Opiates only[a]		Non-Opiates[b]	
Frequency of abuse	Nal	Meth	Nal	Meth
Very rare (≤ 10%)	50%	10%	43%	89%
Rare (11 - 25%)	37%	37%	27%	10%
Occasional or more (>25%)	13%	53%	30%	0%
Mean % positive tests	15%	32%	16%	3%

a $X^2 = 11.51$; df = 2; $p < .01$. t-test of mean difference = 3.92; df = 47; $p < .001$. Excludes quinine; includes methadone for naltrexone group.

b $X^2 = 11.23$; df = 2; $p < .01$. t-test of mean difference = 3.25; df = 47; $p < .01$. Excludes quinine, includes amphetamines and barbiturates.

TABLE 2

COMPARISON OF URINE RESULTS FOR SHORT-TERM (1-8 WEEKS) NALTREXONE PATIENTS WITH A MATCHED GROUP OF METHADONE PATIENTS (NAL=40; METH=30)

	Opiates only[a]		Non-Opiates[b]	
Frequency of abuse	Nal	Meth	Nal	Meth
Never (0%)	35%	20%	52%	70%
Occasional (≤50%)	52%	43%	35%	27%
Often (>50%)	12%	37%	12%	3%
Mean % positive tests	25%	45%	23%	11%

a $X^2 = 6.03$; df = 2; $p < .05$. t-test of mean difference = 2.71; df = 68 $p < .01$. Excludes quinine; includes methadone for naltrexone group.

b $X^2 = 2.93$; df = 2(ns). t-test of mean difference = 1.86; df = 68(ns). Excludes quinine, includes amphetamines and barbiturates.

which the patient had one or more positive urine tests by the total number of weeks in which at least one urine was obtained. An index of 100 indicates a positive urine for every week tested, 50 indicates a positive in half the weeks tested, and zero indicates no documented use. The short-term patients showed more evidence of street opiate use, but even the long term patients continued to use opiates at a fairly steady rate despite the presence of naltrexone. Interestingly, the use of non-opiates seemed to decrease over time (graph 3). Perhaps the non-opiates (barbiturates, amphetamines) were being used early in treatment as an attempt at self-medication while patients were getting adjusted to naltrexone.

Ancillary prescription medication was discouraged after the first week, but 10% of the patients were treated for varying intervals with minor tranquillizers and two were treated with amitriptyline.

Long term patients had better working relationships with their counselors and participated in individual and group therapy more regularly. Most of them were considered "good" patients by the staff. They were cooperative and "well motivated," in contrast to the early dropouts, many of whom were felt to be uncooperative, challenging, and unreliable. Four patients initially thought to be "bad" remained in treatment more than four months and showed marked improvement in their behavior. Those with drug-free friends and those who moved away from neighborhoods associated with drugs stayed in treatment longer and had better outcomes.

4. Multiple treatment episodes and irregular attendance:

Thirty-one of the 142 patients underwent two or more distinct treatment episodes, in which at least one month elapsed between doses of naltrexone. One patient was treated on three occasions for a total of four distinct episodes for a total of 13% months. Those with more than one treatment episode were using opiates several times a week or were physically dependent when they returned. When a patient was conflicted about restarting naltrexone, or when he was missing doses frequently, staff asked him to "make a decision" to take naltrexone regularly or choose another type of treatment. Three patients with poor attendance signed contracts agreeing to attend regularly, but this had little effect. One who took naltrexone for three and a half months missed medication almost once a week, and another treated for seven months missed one or two days a week on several occasions. The first patient used opiates when he missed, but the second did not.

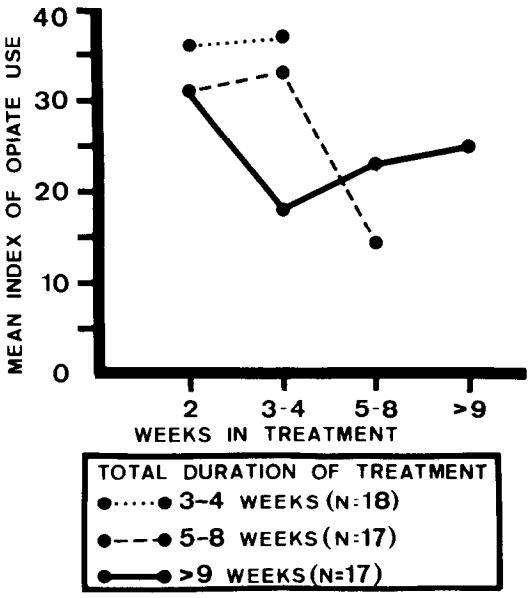
Reasons for missing medication varied. Some patients wanted to "feel" heroin and returned to treatment to prevent readdiction. Others, especially later in treatment, wanted to test themselves to see whether they could resist narcotics when not protected by naltrexone. In general, those who stayed in treatment longest had the best attendance records and planned termination more carefully.

5. Medical findings

Only three significant medical conditions developed in the course of 179 treatment episodes. One patient with chronic recurrent hepatitis and episodic alcoholic intake had an elevated bilirubin which peaked at 3.4 mg% in the third month of treatment and returned to 1.2 mg% at termination, five and a half months after starting naltrexone. A medical consultant diagnosed subclinical hepatitis.

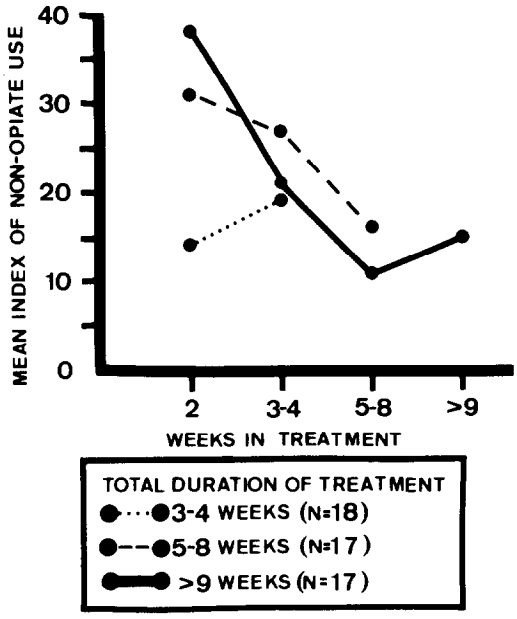
GRAPH 2

MEAN INDEX OF OPIATE USE OVER TIME FOR THREE GROUPS OF PATIENTS DIFFERING IN DURATION OF TREATMENT



GRAPH 3

MEAN INDEX OF NON-OPIATE USE OVER TIME FOR THREE GROUPS OF PATIENTS DIFFERING IN DURATION OF TREATMENT



One patient took naltrexone 13% months and developed Idiopathic Thrombocytopenic Purpura (ITP) and another developed an allergic skin rash after six weeks of treatment (see case histories).

Laboratory values, EKG's and chest X-rays remained within normal limits for most patients. There were fluctuations in liver function studies and in the percentage of lymphocytes but no patterns were evident, and values were similar to those found in methadone patients. Eleven patients had transient non-specific ST-T wave changes in EKG tracings. Two patients with Wolff-Parkinson-White syndrome were treated for two and four months respectively and had no EKG changes or cardiovascular symptoms. Eleven had blood pressure increases of five to 10 mm diastolic and/or systolic over baseline recordings taken at rest in the hospital. Two hypertensive patients were evaluated medically and treated for hypertension during the study. The first took methyldopa as prescribed and had well controlled blood-pressures. The second was treated on three occasions for a total of three and a half months. He took antihypertensive medication irregularly and did not adhere to his diet. His pressures were poorly controlled before, during, and after treatment with naltrexone and ranged from 130/85 to 160/110.

Five patients were terminated because of concurrent medical problems. Naltrexone was discontinued twice in the patient with poorly controlled hypertension. One woman dropped out during a recurrence of a renal infection. A patient with a history of drinking and gastric ulcer, in remission, began drinking after induction and developed gastritis. He was readmitted to the hospital, naltrexone was stopped, anti-acids and a special diet were ordered, and epigastric distress subsided in two days. The last two cases are presented below:

Case History #1

GS is a 24 year old single white male who took naltrexone in four distinct treatment episodes

for a total of 13½ months. He had an exacerpation of acne during his first induction onto naltrexone in April, 1974, and suffered a head injury playing ice hockey prior to his third induction in April, 1975, but otherwise did well in treatment and had no medical complications. He was drug free for several weeks after each treatment episode, but reverted to opiate use each time. He began naltrexone for the fourth time on February 19, 1976. He complained of weakness and lethargy during the first ten days of treatment, but then felt well. The patient was hit in the jaw playing hockey on March 5 and his mouth swelled. The next day he drained the swelling with a syringe. Gne day later "spots" appeared on his tongue and shoulders. He took two doses of penicillin and one dose of tetracycline that evening because he thought he had infected himself. On March 8 he came to the clinic and hemorrhagic bullae were seen on his tongue and oral mucosa, there was a right mandibular dental cyst, and petechiae were present over his arms and legs.

GS was admitted to the hematology service of the VA Hospital and bloodwork revealed a platelet count of 2000/cu mm. Hemoglobin had dropped from a baseline of 14.6 gm% to 13.5.Reticulocyte count was 2%. White count was 7,300 with 68% neutrophiles, 22% lymphocytes, 3% eosinophiles and 7% monocytes. No atypical lymphocytes were seen and a mono spot test was negative. Serum electrophoresis was within normal limits. Mouth X-ray showed a dentigious cyst behind a partially impacted right lower third molar. Bone marrow was normal. Idiopathic Thrombocytopenic Purpura was diagnosed and Prednisone 60 mg daily was started. By March 17 the platelet count returned to 22O,000/cu mm and petechiae subsided. The last naltrexone had been 150 mg. on March 5. The patient denied drug use during this treatment epidose and all urines were negative for drugs.

GS was discharged from the hospital on March 17. Prednisone was gradually lowered and it was discontinued at the end of April. The patient is currently being followed in drug-free counselling and his platelet count has remained within normal limits.

Standard antigen-antibody assays conducted at the University of Pennsylvania did not show a causal relationship between naltrexone and lowered platelet count. Experimental assays of radiolabled serotonin release, the amount of immunoglobulin (IgG) on platelets, and antiplatelet activity in the patient's serum were inconclusive. The Hematology service felt the clinical course was compatable with either ITP or drug induced immune platelet destruction.

Since ITP may follow viral infections, serum for viral studies was collected while GS was in the hospital and after discharge. None of the titers indicated an acute viral infection, although the lethargy during the first ten days of the last treatment episode may have been related to an undetected infection. ITP may also occur after bacterial infections. The patient's manipulation of the mandibular cyst on the day prior to developing hemorrhagic bullae may have caused an infection, but blood and throat cultures were negative.

Case History #2

RH is a 25 year old single veteran who has used opiates for seven years. He started naltrexone on February 17, 1976 and did well with no street drug use (urine verified). On March 27 he developed a sore throat and fever to 102° F. Two days later a skin rash with intense itching appeared on his lower extremities, forearms, and anteriorly over both shoulders. His last dose of naltrexone had been 150 mg on March 26.

MR. H. was admitted to the hospital where throat cultures grew out alpha streptococcus and neisseria. Blood count showed 14,200 white blood cells with 75% neutrophiles, 15% lymphocytes, 5% eosinophiles, and 5% monocytes. No atypical lymphocytes were seen. Liver enzymes were normal and bilirubin was 1.5 mg%. Medical and dermatologic consultants felt the clinical picture was strongly suggestive of a morbilliform drug eruption with features of serum sickness. Skin biopsy showed a nonspecific dermal infiltrate of lymphocytes and polymorphonuclear cells.

The patient was treated with Periactin for pruritis and by March 31 was afebrile, his sore throat subsided, and the rash resolved. He was discharged asymptomatic on April 1 and was treated in drug free counselling. He did well until April 7 through 10 when he used six bags of heroin each day. He returned to the clinic on April 12 and requested naltrexone. RH was readmitted to the hospital and was given 1 cc of naltrexone placebo in juice on April 12 and 13. A low dose naloxone test on April 13 was negative (0. 1 cc intradermally followed by 1.0 cc IM). At 4:00 pm on April 13 he was given 5 mg of naltrexone and was observed overnight. On April 14 ten mg of naltrexone was given at 8:00 am and 20 mg was given at noon. Erythema and pruritus of both palms appeared at 8:00 pm on April 14 but subsided by the following morning. No further naltrexone was given. On April 20, six days after the last naltrexone exfoliative dermatitis of the palms and fingers of both hands began and lasted for a total of six days. Medical and dermatology services considered the

erythema, itching, and exfoliative dermatitis of the hands to be confirmation of an allergic skin reaction and serum sickness. The patient began using opiates heavily two weeks after stopping naltrexone and is presently in treatment with methadone maintenance.

Termination and follow-up:

Patients were encouraged to consider treatment for a minimum of two months. They were told that the longer they took naltrexone, the better their chances of preventing relapse to narcotics. Planned terminations and supplementary drug-free therapy were discussed in counselling sessions. Nevertheless my patients, particularly early dropouts, left treatment prematurely and failed to tell staff in advance. No patients reported difficulties when stopping naltrexone and none described withdrawal symptoms. Some who were stabilized on naltrexone reported opiate blockade for up to six days after stopping naltrexone, but this was not verified in the clinic.

A follow-up study was begun in November, 1975. Patients were seen by a follow-up counselor during screening, and addresses and telephone numbers were verified. Interviews were scheduled one and six months after stopping naltrexone. Twenty-six of 30 scheduled patients (87%) were contacted at the one month mark and 19 of 25 (76%) were seen at six months. Forty-four urines were collected in 45 interviews (98%). The results of the follow-up urines are shown in Table III. The percentage of patients opiate free was the same at both 1 month and 6 month Follow-ups.

Discussion:

Naltrexone may have a place in the step-wise treatment of opiate users as described by Goldstein (1976). Many patients did well in treatment and some seen for a relatively short time apparently benefited from it. But naltrexone appeals to a small percentage of patients. Careful screening for "well motivated" subjects would increase the retention rate, but would eliminate the possibility of evaluating antagonists across the broad spectrum of patients seen in a drug treatment clinic. In fact several poor risk patients did extremely well. The decision to begin induction of naltrexone two to four days after methadone was based on earlier experience with cyclazocine in which patients complained about the length of time they had to stay in the hospital to be stabilized on cyclazocine. Naloxone is predictive of the degree of withdrawal to be expected following 10 mg of naltrexone orally. It is, therefore, useful in avoiding severe prolonged symptoms which might otherwise occur in vulnerable patients.

Even when minimal or no withdrawal symptoms are observed when starting naltrexone, the dropout rate is high. Since naltrexone is nonaddicting and has no reinforcing qualities in itself, patients can stop easily by missing several doses. Longer acting forms of naltrexone are being developed, but patients wishing to return to opiates would only have to wait longer for the antagonist effect to disappear. Our impression is that the quality of counseling affects time in treatment and outcome. Counseling, therefore, should be incorporated into studies of longer-acting antagonists.

From a medical point of view, naltrexone appears safe and nontoxic. In the patient with Idiopathic Thrombocytopenic Purpura, a causal relationship was not clearly shown. Why sensitivity to naltrexone should develop after 13% months and four treatment episodes is not understood. ITP may follow viral infections and it is possible that a viral illness was present during the first ten days of this treatment episode. ITP may also follow bacteral infections and it is conceivable that this patient may have infected himself when he drained the mandibular abscess. In the patient with an allergic skin rash and serum sickness, a causal relationship between naltrexone and the condition seems to be supported. Restarting naltrexone was followed by palmar erythema and itching and exfoliative dermatitis of the Fingers and palms. No other allergic or toxic manifestations with naltrexone have been reported.

The degree of street opiate use seen in patients taking naltrexone was somewhat surprising. It was still significantly less than that seen in methadone patients matched For time in treatment, but the degree of street opiate use was greater than that noted in some prior antagonist studies (Kleber, 1974; O'Brien, 1375). The urine tests used here (RIA) were quite sensitive and the false positive rate has been low. The lack of extinction of this behavior (Graph 2) seen over 9 weeks suggests that longer term treatment should be conducted.

The follow-up study though based on a small sample is encouraging, and indicates that longer term treatment is associated with better out-come. A high proportion of follow-up evaluations after termination is feasible and we intend to continue this procedure until an adequate sample is obtained. All antagonist programs should have follow-up and tracking of terminated patients built into the project. Comparisons with other modalities such as therapeutic community and methadone could provide clinically useful information.

TABLE 3

POSITIVE URINES FOR OPIATES AFTER TERMINATON OF NALTREXONE TREATMENT AS A FUNCTION OF TIME IN NALTREXONE TREATMENT (N=44)

Time in Treatment	Positive	Opiate-free
<1 week (N=16)	81%	19%
1-8 weeks (N=19)	74%	26%
>8 weeks (N=9)	22%	78%

$X^2 = 8.39$; df = 2; $p < .025$

1. Follow-ups were done at one month (N=25) and six months (N=19). Twelve patients were in treatment at the time of follow-up; thirty-two were not. Differences in urine test results did not approach significance and were negligible. Accordingly, results as a funtion of these factors have been pooled in the table.

2. Positive urine tests for abusable non-narcotic drugs (amphetamines, barbiturates, or quinine only) have been included in the opiate-free column. Three such results were obtained, one in each length-of-treatment group.

3. Three patients are included in the table twice. Two of these had two distinct treatment episodes and two follow-up interviews. One was followed up at both one and six months after a single treatment episode. Seven patients were in methadone maintenance treatment. Six of them had positive tests for morphine. All seven are included in the positive column.

4. One patient in the 1-8 week group was in prison at the time of follow-up and is included in the Opiate-free column.

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COMPARISON OF TWO NALTREXONE TREATMENT PROGRAMS: NALTREXONE ALONE VERSUS NALTREXONE PLUS BEHAVIOR THERAPY

Edward Callahan, Ph.D., Richard Rawson, Ph.D., Michael Glazer, M.A., Beverly McCleave, B.A., Richard Arias, B.A.

The H.A.L.T. Project is a heroin addiction research and treatment program funded by NIDA through UCLA. H.A.L.T. is an acronym for Heroin Antagonist and Learning Therapy. The primary goal of this three-year project is to compare the effectiveness of naltrexone, behavior therapy and a combination of the two as outpatient treatments for heroin addiction. While some data from the behavior therapy group will be presented, the primary focus of this paper is an evaluation of naltrexone alone as a singular treatment intervention as compared to naltrexone in conjunction with a comprehensive behavioral treatment program.

DEMOGRAPHIC ANALYSIS

The H.A.L.T. Project is located in Oxnard, California. Oxnard is located on the Pacific Coast, approximately fifty miles north of Los Angeles. Oxnard is the largest city in Ventura County, an agriculturally based area of 450,000 people. Approximately 60,000 Mexican-American/Chicanos live in Ventura County with 30,000 or roughly one-half living in Oxnard. There are 8,000 Blacks who live in the county, and about 80% of them live in Oxnard.

From December 1, 1974 until May 1, 1976, 167 potential subjects Filled out a brief one-page first contact intake sheet. Completion of this sheet resulted in the random assignment of the potential subject to one of the three treatment groups. Subjects had to be male, at least eighteen years of age, and using heroin for at least one year. Table 1 illustrates the distribution of the 167 subjects according to ethnic group and treatment group assigned. Table 2 presents the mean age, edu-

cational level, age at first use of heroin, and numbers of years addicted to heroin, according to ethnic group. These data were collected on 57 people or 34% of the subjects assigned, since many of the subjects never returned to complete the background information questionaire. Currently this information is being collected at the initial contact in order to make data collection more complete.

A comparison of the three ethnic groups on the four measures listed in Table 2 indicated that there were no significant differences on these background measures ($F<1$, in all cases). Therefore, a summary description of the subjects who have participated at H.A.L.T. is as follows: ethnically, the population is 52% Chicano, 40% White and 8% Black; the mean age is twenty-six; the mean educational level is eleventh grade; the mean age of First heroin use is eighteen; and the mean length of heroin addiction is eight years.

PROGRAM DESCRIPTION

In order for a subject to earn the services and benefits offered by the program, it is necessary to complete a two week entry probation period, as outlined by a contingency contract. The purpose of the first week of this probation is to detoxify the subject, using either an inpatient detoxification hospital unit or by using outpatient medication. During the second week, the first seven doses of naltrexone are taken and the therapy program is initiated. IF a subject completes a required amount of the contracted responsibilities and takes all seven doses of naltrexone, he earns active client status.

Following completion of the entry probation requirements, subjects begin a six-week stabilization phase. During this treatment phase the naltrexone schedule consists of 50 mg. doses Monday through Friday, a 100 mg. dose on Saturday and no dose on Sunday.

There are three treatment goals for subjects in the naltrexone/behavior therapy group during this period. The first is establishing a consistent naltrexone taking schedule. Second, a coordinated behavior therapy program is started. This program contains three main parts. First, contingency contracting is used to structure the treatment program. Each subject is always on contract, and the contracts are used to structure program responsibilities, acceptable levels of performance, and steps to achieve life goals. Secondly, subjects make multiple daily data phone calls to the project. This aids in identifying subject problem areas and in keeping in close contact with the subjects. Last are the actual behavioral technologies, which tend to be divided into two parts. First, thought stopping, covert sensitization and assertion training are used to aid the subject in staying away from heroin use, lifestyle behaviors and contacts. Second, deep muscle relaxation, assertion training and life management training, which involves getting the client to engage in new social and recreational activities, are used to guide the subjects into a new drug-free lifestyle. Finally, it is expected that at the end of the six-week stabilization period all subjects will be employed or in school.

Subjects in the naltrexone alone group are expected to demonstrate regular naltrexone taking behavior and to obtain employment or an educational placement, but are not exposed to

TABLE 1

Number of Clients Assigned to Each Treatment Group

	Ethnic Group			
	White	Black	Chicano	Total
Behavior Therapy	32	7	32	71
Naltrexone	18	4	24	46
Naltrexone/Behavior Therapy	13	3	34	50
Total	63	14	90	167

TABLE 2

Demographic Characteristics

	Ethnic Group		
	White	Black	Chicano
$\bar{X}$ Age	24.9	30.7	25.8
$\bar{X}$ Education	11.5	11.2	10.3
$\bar{X}$ Age First Use of Heroin	18.9	17.7	17.5
$\bar{X}$ Years Addicted to Heroin	6.3	12.7	8.3

TABLE 3

Percentage of the 167 Subjects Achieving Active Client Status

	Ethnic Group			
	White	Black	Chicano	Total
Behavior Therapy	29%	13%	15%	21%
Naltrexone	44%	33%	26%	33%
Naltrexone/Behavior Therapy	69%	66%	12%	30%
Total	41%	28%	17%	27%

any of the behavior therapies. In all phases at least three supervised urine specimens are taken per week.
Following the stabilization phase subjects begin a four to six month maintenance phase. During this treatment phase, the naltrexone schedule is 100 mg. on Monday and Wednesday and 150 mg. on Friday. Subjects in the naltrexone/behavior therapy group are seen in therapy for approximately one hour each time they receive their naltrexone dose. Subjects in the naltrexone alone treatment group merely receive their naltrexone and give urine specimens. The naltrexone alone subjects usually remain at the project for short periods of time for staff social contact, which appears to be very important for many of them. If they request personal counseling, they are referred to local mental health agencies.

As of May 1, 1976, only one subject had progressed past the maintenance phase into the pre-graduation phase. During the pre-graduation phase, most naltrexone subjects will begin a thirteen-week fading schedule. They will alternate weeks on an off of naltrexone, gradually increasing the time off of naltrexone. This will give them the opportunity to experience drug urges and life stresses without being opiate-blocked although still in contact with the program. If, at the end of this thirteen-week period there have been no opiate positive urines, the program will have successfully been completed. While this may be varied for individual subjects, it is the tentative program which subjects expect.

CLIENT PERFORMANCE

Probationary Period

Out of the 167 subjects assigned to a treatment group, 45 or 27% have earned active client status. The percentage of subjects earning active status computed in terms of treatment group by ethnic group is shown in Table 3. It should be noted that two White, one Chicano and one Black subject were reassigned from the naltrexone group to the behavior therapy group for medical reasons.

As shown in Table 3, 21% of the behavior therapy group subjects, 30% of the naltrexone/behavior therapy subjects and 33% of the naltrexone alone group subjects were successful in earning active client status. An X^2 analysis of these data indicated that the success rates were not significantly different, based on treatment group assignment (X^2 = 2, 2.25, df = 2, P>.1).

The success of subjects in earning active status significantly differs according to ethnic group. As shown in Table 3, 41% of the Whites, 28% of the Blacks and 17% of the Chicanos were successful in earning active client status. An X^2 comparison indicated that the difference is highly significant (X^2 = 11.27, df = 2, P<.01). While the number of Black subjects (n=14) is too small to be conclusive, the number of Whites (n=63) and Chicanos (n=90) suggests that it is more difficult for Chicano subjects to earn their way into the H.A.L.T. Project than for White subjects. This difference is particularly striking in the naltrexone/behavior therapy group, where 69% (9 of 13) of the White subjects earned entry, while only 12% (4 of 34) of the Chicanos were successful.

One possible reason for the difference in entry success rates between Whites and Chicanos is the ethnic makeup of the H.A.L.T. staff. There are one White, one Black and two Chicano counselors on the staff. However, the director, research coordinator, clinical coordinator and administrative assistant are all White. Also, the area's Chicano heroin subculture appears to be much larger, more complex and more reinforcing than the local white heroin subculture. It is also possible that there are background variables other than race which differentiate the two populations. Although there were no differences in the background variables listed in Table 2, a more detailed analysis of background including drug history, family makeup, legal history and experience with other drugs, may provide some additional information concerning the White/Chicano entry success differences.

NALTREXONE TAKING BEHAVIOR

Ninety-six people have been scheduled to start naltrexone between January 1975 and May 1, 1976. As shown in Figure 1, fifty subjects were assigned to naltrexone and forty-six to naltrexone/behavior therapy. Of these ninety-six subjects, 14 of 50, or 28% of the naltrexone subjects took a first dose, and 15 of 46, or 33% of the naltrexone/behavior therapy subjects took a first dose. This suggests that approximately 30% of all subjects scheduled to take naltrexone actually took a first dose. Before discussing the successful 30%, the 70% who were not successful will be discussed.

Of the 50 assigned naltrexone subjects, 20 had no contact with the program following the initial contact. Gut of these 30 subjects in the naltrexone group who attempted to enter the program: 7 were medically ineligible. Therefore, in the naltrexone alone group, 14 of 23 or 61% of the subjects who attempted to start the drug did take a first dose. In the naltrexone/behavior therapy group 32 of the 46

assigned subjects returned for a second contact. Of these 32, 2 were medically ineligible. Therefore, of the 30 subjects who attempted to start naltrexone in the naltrexone/behavior therapy group 15 of 30, or 50% were successful. Overall, 53 eligible subjects made an active attempt to begin naltrexone and 29 or 55% did take a first dose.

As of May 1, 1976, the average length of time on naltrexone for the 29 subjects who took a first dose was 65.2 days. However, as shown in Figure 1, there was a substantial difference between the naltrexone alone and naltrexone/behavior therapy group. The mean number of days on naltrexone for the naltrexone alone group is 44 days, while for naltrexone/behavior therapy the mean duration is 85 days. Figure 2 presents the total number of days on naltrexone for each of the 29 subjects. The dotted line which extends across the entire panel for each treatment group indicates the mean number of days on naltrexone for each group. The dotted lines within each of the bars indicates stops and restarts on naltrexone for that subject. The bars with horizontal lines represent subjects who as of May 1 were still receiving naltrexone.

A t-test comparison on the difference between the two groups mean durations on naltrexone could not be computed due to extreme heterogeneity of variance. However, the Wilcoxin Rank Sum Test indicates that the duration of days on naltrexone is significantly higher for subjects in the naltrexone/behavior therapy group than for subjects in the naltrexone group ($P<.025$). It is clear, therefore, that the duration of time on naltrexone can be increased significantly by the concurrent involvement of the subject with a comprehensive behavior therapy treatment program.

URINALYSIS

Figure 3 illustrates urine results from December 1, 1975 to May 1, 1976 for active clients in each of the three treatment groups. During this five month period, 14 of 102 urine samples or 13.8% were opiate positive for subjects in the behavior therapy group. In the naltrexone group, 6 of 131 or 4.6% of the urines were positive for opiates and 8 of 259 or 3.1% of the urines were opiate positive for subjects in the naltrexone/behavior therapy group. A comparison of these urine results indicated that there was a significant difference between the groups in ratio of opiate negative to total urines given ($X^2 = 15.79$, df, $P<.01$). The source of this difference results from a significantly greater number of opiate-positive urines occurring in the behavior therapy group than in the naltrexone groups.

EMPLOYMENT/SCHOOL DATA

Figure 4 presents the percentage of subjects either employed or in school upon entering H.A.L.T. (Pre), and at last contact (Post). This data is only for those subjects who earned active client status. The number of subjects per treatment group is: behavior therapy - 22, naltrexone - 14, naltrexone/behavior therapy- 15. As shown by Figure 4, there is a substantial increase in employment or school for subjects in all three treatment groups during their involvement at H.A.L.T.

NALTREXONE-MEDICAL & SAFETY CONSIDERATIONS

There are three areas of medical and safety considerations which are important to review: factors affecting medical/psychological eligibility; problems insuring subjects are opiate-free prior to administration of the first dose; reported symptoms and physiological functioning of subjects while taking naltrexone.

FACTORS AFFECTING ELIGIBILITY

As reported above, 9 out of 96 subjects examined were medically or psychologically ineligible to begin naltrexone. The disorders which produced these ineligibilities were: two cases of diabetes; two abnormal EKG's; one case each of active hepititis; a nephrectomy; Myasthenia Gravis; Valley Fever (Coccidiodomycosis); and a psychiatric diagnosis of borderline schizophrenia. Since these cases represent less than 10% of all persons scheduled to begin naltrexone, it seems reasonable to conclude that medical ineligibility does not appear to hamper the usefulness of naltrexone as a treatment for heroin addiction. It should be noted that all of these subjects were allowed to earn their way into H.A.L.T. and receive therapy as non-research behavior therapy subjects. Four of these nine subjects achieved active status.

PROBLEMS INVOLVING FIRST DOSE

The major problem in preparing subjects for their first dose of naltrexone has been to keep subjects opiate-free for five days prior to the first dose. Two methods have been

FIGURE 1

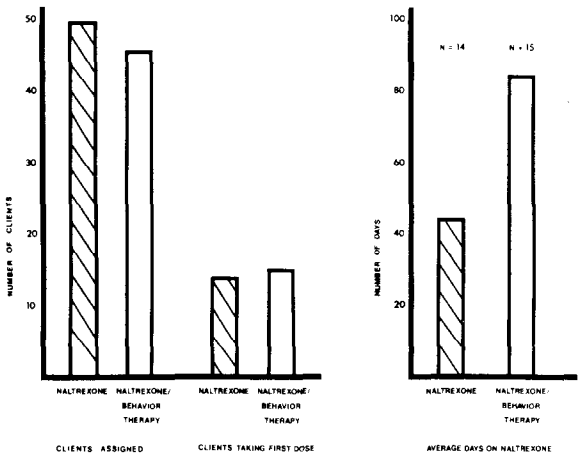

Figure 1. Left panel, number of clients assigned to take dose of naltrexone and number of clients receiving the first dose. Right panel, mean number of days on naltrexone for each of the groups receiving naltrexone.

FIGURE 2

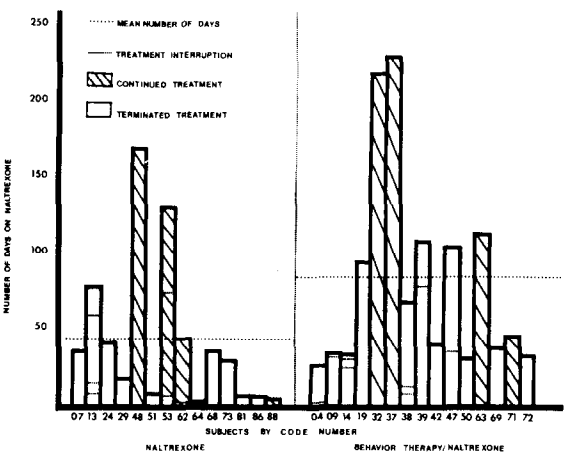

Figure 2. Number of days on naltrexone for each naltrexone and naltrexone/behavior therapy client.

FIGURE 3

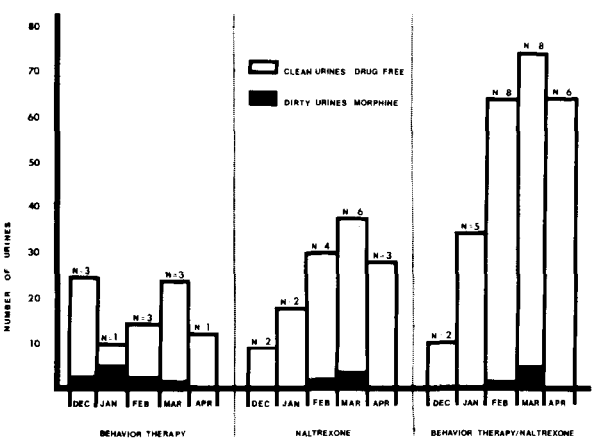

Figure 3. Five months of urinalyses for each of the three treatment groups.

FIGURE 4

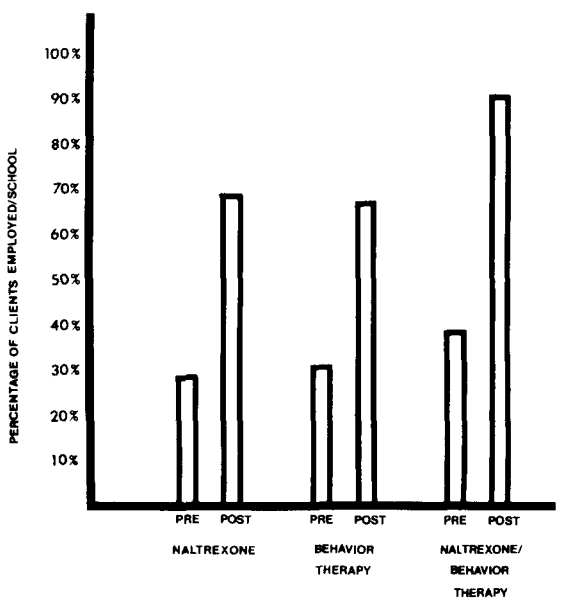

Figure 4. Percentage of subjects employed or in school before contact with H.A.L.T. (Pre) and at last contact with H.A.L.T. (Post).

used to accomplish this., The first, and most certain method has been to have subjects com-- plete a seven-day detoxification - program at an inpatient detoxification center in Palmdale, California. The detoxification program at Palmdale typically uses six days of methadone to detoxify heroin addicts. However, H.A.L.T. subjects are given arm bands to wear and have special notation on their records to insure that they receive methadone for the first two days only. They are then administered Darvon-N, Valium and Chloral Hydrate to complete the last five days of detoxification. This insures that on the day they leave the detoxification center they have been opiate-free for five days. The Palmdale detoxification staff understands the purpose of naltrexone and the need for five opiate-free days. Transportation to and from the detoxification unit is provided by the H.A.L.T. Project to reduce the number of subjects who fail to return directly from Palmdale to the H.A.L.T. Project.

Even with these precautions, there have been difficulties with this method. The most common problem is that a substantial number of subjects do not complete the detoxification program, even though they have contracted with H.A.L.T. to do so. Also, there has been one case of a sympathetic nurse giving a subject a dose of methadone on the sixth day of detoxification. Had the subject not reported this methadone use prior to his scheduled first dose of naltrexone, it could have resulted in a naltrexone-induced withdrawal reaction.

Although there have been difficulties in using an inpatient detoxification program, the problems involved with outpatient detoxification have been far worse. This approach is sometimes used for clients who are not able to go to Palmdale due to work, family or other reasons. In a majority of these cases, Dalmane and Valium have been used as prescribed by the local substance abuse program to produce a five day "clean" period in order to start naltrexone. Three consecutive opiate-free urines are required as evidence that the subject has been opiate-free for five days prior to his first dose. This has been extremely difficult to achieve. This difficulty is particularly evident in subjects with a long history of heroin use.

Due to the problems with outpatient detoxification, subjects scheduled to begin naltrexone are strongly urged to go to an inpatient detoxification center, though this approach is far from a guarantee that the client will eventually start on naltrexone.

Of the 53 medically eligible subjects who attempted to start naltrexone, 29 or 45% of these subjects did not successfully remain opiate-free for five days in order to start naltrexone. In singling out the major factor which has hindered the implementation of naltrexone use at H.A.L.T., it is this problem of detoxification in order to begin naltrexone.

REPORTED SYMPTOMS AND PHYSIOLOGICAL FUNCTIONING

H.A.L.T. naltrexone subjects have reported a variety of physical symptoms. The most common have been stomach cramps, decreased sexual potency, irritability, anxiety, low energy, and difficulty sleeping. Six subjects reported discontinuing naltrexone due to physical side-effects. Of these six subjects four reported discontinuing due to severe stomach cramps, one due to decreased sexual potency, and one due to frequent nosebleeds. This last subject later reported that the nosebleeds had occurred prior to starting naltrexone, and continued after its discontinuation. He later restarted naltrexone and has reported no recurrence of the nosebleeds.

By far the most common symptom has been stomach cramps. Although only four subjects have discontinued naltrexone due to stomach cramps, many subjects have reported them. One suggestion given to subjects has been to eat before taking their dose. Some alleviation of stomach cramps has occurred when subjects ate prior to taking a dose of naltrexone. Subjects who begin naltrexone after heavy heroin use tended to report more frequent and more intense stomach cramps.

The only other symptom which has been reported with any frequency is decreased sexual potency. One subject discontinued naltrexone for this reason. Shortly thereafter, a number of reports of decreased sexual potency occurred. These reports were predominantly from acquaintances of the subject who discontinued due to problems in sexual potency. The subjects were reassured that there had been'no prior research to show that naltrexone affected sexual functioning. Within two weeks these subjects all reported normal sexual functioning.

Three subjects were taken off naltrexone when naltrexone could not be ruled out as a factor in their three different medical problems. One case of high blood pressure, one case of severe weight loss and one case of a developing Cataract resulted in the discontinuation of naltrexone on the order of the staff physician. Although in the cases involving high blood pressure and weight loss there had been a prior history of these problems, it was felt by the staff physician that discontinuation was necessary. In the case of the subject who developed a cataract, there had been an eye

injury immediately prior to the development of this condition. While the staff physician was reasonably certain that naltrexone was not involved in this condition, the subject was discontinued as a precaution against the possibility that naltrexone might worsen the cataract.

A review of the physical examination data shows no systematic changes in physiological functioning. There have been no changes in hematology reports, medical urinalysis, electrocardiogram reports, or chest x-ray reports. Daily blood pressure readings have shown no systematic changes for any clients. In short, except for the cases reported above, there have been no adverse physiological effects detected from naltrexone use.

One last incident which bears on the medical/ physiological aspects of naltrexone concerns the possibility of flushing naltrexone out of the body with large quantities of fluids. One subject reported that he could take a 150 mg. (3 day) dose on Friday night, drink a quart bottle of vinegar, then drink a large amount of beer, shoot and feel the effects of heroin by the middle of the third day. He would follow this with more vinegar and beer in order to take his dose of naltrexone and not experience naltrexone-induced withdrawal. He reported having accomplished this on three occasions. The question raised by this report is, can naltrexone be flushed out of the system with large quantities of fluid? If there is evidence of this occurring, w-ill an increased dosage make this technique less effective?

DISCUSSION

One year's experience with naltrexone at the H.A.L.T. Project has confirmed that naltrexone is a viable outpatient treatment for heroin addiction. Although there are a variety of ways to measure the effectiveness of naltrexone as a treatment, the most critical data, the follow-up data are still to be collected.

Therefore, while no final statement can yet be made on the long-term effectiveness of naltrexone there are a number of conclusions which can be reached based on the data collected at H.A.L.T.

The difference in the number of days on naltrexone between the naltrexone group and naltrexone/behavior therapy group is an important finding. This comparison clearly indicates that naltrexone taking behavior can be maintained for a longer period with the concurrent involvement in a behaviorally oriented treatment program.

A survey of subjects' attitudes toward naltrexone suggests that participation in the naltrexone/behavior therapy group promotes a different attitude toward naltrexone than the attitude held by subjects who are in the naltrexone alone group. Subjects in the naltrexone/behavior therapy group view naltrexone as an aid in staying opiate-free while they attempt a change in lifestyle, habits and friends. This is an attitude which is presented and reinforced by the staff and the nature of the behavior therapies used.

Subjects in the naltrexone group view naltrexone more as a "medication" for heroin addiction, which if taken for a period of time will produce a "cure" for heroin addiction. Even though subjects in the naltrexone group are encouraged to make changes in their lives while taking naltrexone, the lack of a structured therapeutic program results in a more passive acceptance of naltrexone as a "cure". Currently data are being collected to document these attitudinal differences and to document whether these attitudinal differences are accompanied by actual changes in relevent behavior.

Another important consideration which has seriously affected the usefulness of naltrexone is the problem of detoxification and preparation for the administration of the first dose of naltrexone. Approximately 45% of all subjects attempting to begin naltrexone fail. It is proposed that a one to two week inpatient program in which to detoxify subjects and initiate naltrexone would be more successful. In this facility, detoxification could occur. followed by the initial doses of naltrexone with an intensive orientation to the behavior therapy program. Using this facility. a realistic attitudinal set toward naltrexone and behavioral techniques could be fostered, and then transferred into the outpatient setting.

Finally, H.A.L.T. analysis of subjects earning entry into H.A.L.T. shows a significant difference in success rates between Whites and Chicanos. At this point it is impossible to document the reasons for this difference. Although the ethnic composition of the H.A.L.T. staff may be a factor in this difference, it is likely that there are profound socio-cultural differences in attitudes toward drug use. Currently, more extensive data are being collected from subjects upon initial contact with the program. These data may help to identify factors which affect the different entry and attrition rates.

In summary, during a period of one year naltrexone was given to twenty-nine subjects.

Fifteen of these subjects concurrently participated in a comprehensive behavior therapy program.

The subjects in this naltrexone/behavior therapy group were maintained on naltrexone for nearly twice as long as naltrexone group clients who received no therapy.

If the chances for readdiction are reduced by increased time on naltrexone, then the data states that naltrexone should be dispensed as part of a broader therapeutic strategy. Follow-up data, which will be collected during the next year will test the validity of this hypothesis.

ACKNOWLEDGMENTS

This work was supported by NIDA Grant DA-01059-02. The authors would like to thank Robert P. Liberman, M.D. for assistance and constructive criticism of this work. Thanks also go to Nancy Thornton for her expert technical assistance. In addition, thanks go to Daniel Dominguez, Daniel McNally and Marcie Chavez for their efforts.

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NALTREXONE IN THE MANAGEMENT OF HEROIN ADDICTION: CRITIQUE OF THE RATIONALE

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INTRODUCTION

We are conducting an experimental trial of a new approach to the use of naltrexone in the management of heroin addiction. Street addicts are first stabilized on a long-acting surrogate opiate, levo-α-acetylmethadol (LAAM) for a period of 1 year. The purpose of this first phase is to buy time, during which the addict can give up heroin use and make the life style changes that are essential to achieving abstinence. After detoxification from LAAM, naltrexone maintenance is offered. A major aim of our program is to teach the patients what naltrexone can do, and to develop their motivation to use naltrexone. The basic rationale of our stepwise approach has been described fully elsewhere (Goldstein 1976), and a preliminary report on the operation of our program has been presented (Wilson and Goldstein 1976). The first patients to detoxify from LAAM are only now beginning the naltrexone phase, so a further progress report is not justified at this time. Instead, I shall use this opportunity to discuss some controversial aspects of the use of naltrexone.

NALTREXONE AND IMPULSIVE USE

The pharmacologic basis of naltrexone therapy is not in question. This antagonist, given in adequate oral dosage (e.g. 120 mg) three times weekly, maintains a sufficient degree of blockade of the opiate receptors to prevent the psychotropic effects of opiate agonists like heroin. Naltrexone itself appears to be without pharmacologic action other than to block opiate effects; thus, it is a drug with virtually no significant toxicity. If naltrexone were taken regularly, the subject would very likely not use heroin (or not continue to use heroin) because heroin would no longer have a positively reinforcing effect. The competitive nature of the blockade, permitting high doses of heroin to override the protection afforded by naltrexone, might be thought to be disadvantageous, because the subject can "cheat" by using more heroin than usual. But this would make little sense, for a simpler and cheaper alternative is available: to omit a dose of naltrexone in order to experience the desired effect of heroin. Naltrexone, therefore, can only work

well if it is taken regularly; in short, it can only work if there is a high degree of motivation to use it (Resnick et al. 1974).

One may well ask, if a subject is sufficiently motivated to use naltrexone, and therefore is presumably strongly desirous of not relapsing to heroin use, why the same motivation would not protect him without the use of an antagonist. The answer is that naltrexone can protect against impulsive use and can prevent the consequences of impulsive use. In this respect, although their pharmacologic actions are very different, naltrexone and disulfiram (Antabuse) share a common rationale. The protective medication is taken at a time when motivation is high, then later, if circumstances arise that would typically lead to use of the agonist drug, there is strong reason to avoid that behavior.

Case histories of recidivist addicts demonstrate the importance of impulsive behavior in initiating relapse. Relapse to heroin use in abstinent ex-addicts is rarely cogitated and planned in advance. Conditioned abstinence ("craving") can be elicited by accidental encounters with active addicts, and can also be produced experimentally (O'Brien 1976). On the street, the victim may experience a helpless feeling of inability to control his own behavior in the events that culminate with a needle in his vein. I recall vividly a staff member in a methadone clinic, who was well maintained on methadone and had been abstinent from heroin for more than a year. This man confessed to me, in a state of agitation, that he had just a few minutes before, in the clinic parking lot, been shown a syringe and needle and offered some heroin, and -- as though in a fugue state -- had "shot up". A former addict had been abstinent for eight years, had moved to another city, had an excellent job, was supporting a family, and was in good financial and social circumstances. One day, quite unexpectedly, he met a former "shooting partner" on the street. Within an hour, he had accepted an invitation to share some "good stuff" -- the start of a downward spiral that ended with a fullblown addiction and the loss of job, family, and possessions. Impulsive heroin use is also often precipitated by a domestic quarrel or other major stress.

Because motivation is the key requireement for possible success with naltrexone, I believe it is futile to expect street addicts to accept and use this drug; yet the major collaborative studies to date on the efficacy of naltrexone have been conducted with just such subjects. No wonder the results have been disappointing. But poor results in a trial doomed lo failure from the start should not preclude attempts to find the right approach. How can we motivate addicts to use naltrexone? Only, I believe, by first helping them achieve life situations as non-addicts that by their own assessments, are worth defending and maintaining. This can not be accomplished miraculously, overnight. Small steps may succeed, where big ones fail. Stepwise progress in rehabilitation is facilitated by short-term support with a surrogate opiate, permitting heroin use to be stopped abruptly without physical or emotional disturbances, while the clinic staff assists with the practical changes that are required in various spheres of life -- health care, employment, education, legal aid, individual and family counselling, housing, breaking away from old "friends", establishing better interpersonal relationships, building a sense of self-worth. We do not know if a l-year period of surrogate opiate support is adequate; perhaps a longer time is needed, as suggested by data on abstinence at follow-up in relation to duration of methadone maintenance (Stimmel and Rabin 1974).

EXTINGUISHING HEROIN-USE BEHAVIOR

It has been proposed (Wikler 1974)) based upon operant conditioning experiments with animals, that heroin-using behavior has to be extinguished actively if an antagonist is to work. If an animal has learned to self-administer an opiate by bar-pressing, and an antagonist is then given, there is a transient increase in bar-pressing followed by gradual extinction, since the reinforcer no longer acts. It is argued, therefore, that addicts should be encouraged to inject heroin while maintained on naltrexone, in order to extinguish that behavior. I believe the analogy is false, in that it discounts the role of cognition in the control of human behavior. We are able to anticipate consequences and to modify our behavior accordingly. Consider one of those seductive Las Vegas gambling machines, the "one-armed bandit". We know from previous experience that by feeding coins into the machine we can sometimes get a payoff, and even occasionally hit a jackpot. Now one day we find an official-looking sign on the machine: "Out of Order". Do we keep feeding coins in nonetheless, as the rat or monkey would do, until eventually, getting no payoff, we extinguish our gambling behavior? Certainly not. If we have good reason to believe the sign (e.g., through a discussion with a maintenance engineer, or through previous conviction that similar signs have been correct), we don't waste even a single coin. Thus, it is not surprising that many subjects taking naltrexone may not use heroin to test and verify the protection (Meyer et al. 1976). The knowledge that naltrexone is in one's system is the sign that says "Heroin Won't Work". In this connection, the observation that naltrexone can diminish

"craving" (Meyer et al. 1976) is entirely understandable, since "craving" is generally elicited by the possibility of obtaining a drug rather than by its unavailability. It follows from this analysis that naltrexone can only work if the patient understands how it works and believes that it will work.

The analysis presented above suggests the possibility that placebo might be just as effective as naltrexone. But this is false logic. On ethical and legal grounds, the use of a placebo cannot be kept secret. And any attempt to compare naltrexone with placebo in an ethical and legal manner (subjects being informed of the possibility of receiving a placebo in a blind design) invites the subject to test by using heroin, thereby not only destroying the supposedly blind design, but also jeopardizing the subject's welfare. I believe that the technique of placebo control is inappropriate in this context, and that data from naltrexone trials that included placebos should be viewed with serious reservations.

ANTAGONISTS AND THE ENDOGENOUS OPIOID PEPTIDES (ENDORPHINS)

Finally, I should like to mention the newly discovered endogenous opioid peptides (endorphins) in pituitary (Teschemacher et al. 1975 ; Cox et al. 1975) and brain (Hughes et al. 1975). Could their existence have some bearing upon the use of antagonists? We know now that the opiate receptors, which are blocked by naltrexone and other antagonists, are really endorphin receptors. It must be assumed that they play some physiologic role in the nervous or endocrine systems. How can we block these receptors without interfering with their normal function? The answer to this question is not yet clear. There seems to be a paradox, in that brain levels of naltrexone (or naloxone) sufficient to block the effects of heroin or morphine do not cause any significant disturbances in lower animals or humans.
There are at least two interpretations. First, it is possible, though unlikely, that an antagonist could block an exogenous agonist more effectively than an endogenous one -- particularly one released very close to the receptors. Second, and more probable, the endorphin system could ordinarily be on a "standby" basis, to be called into play by special conditions like stress or pain. If that were true, one would expect no effects of antagonist unless the endorphin system were first properly activated; we have yet to discover how to do this experimentally.

If we can generalize from the actions of heroin and morphine, we can surmise that endorphins are involved in obtunding pain by the same curious mechanism responsible for opiate analgesia. This "analgesia" is characterized by a profound and generalized alteration of affect, in which indifference to all aversive stimuli (not only pain) occurs. Thus, it is possible that the primary effect of endorphin is to modulate changes of mood and responses to stress. These speculations suggest that we must study the effects of naltrexone in humans more carefully than we have done thus far -- and not only in ex-addicts but in normal subjects as well.

The possibility should be entertained that heroin addiction may cause persistent damage to the endorphin system (through a classical hormonal negative-feedback loop), or even that a preexisting endorphin deficiency could play a role in predisposing some people to opiate addiction, as I suggested several years ago (Goldstein 1975). If and when it becomes possible, by means of immunoassays, to measure endorphin levels in body fluids, we may be able to learn the relationships between the addicted state and endorphin function. We should be prepared to alter our thinking about the appropriate indications for surrogate opiate maintenance and for antagonist maintenance if such studies uncover the existence of an endorphin deficiency syndrome.

ACKNOWLEDGMENTS

The thoughts expressed in this paper reflect the influence of many investigators, but none more than Dr. Richard B. Resnick, whose innovative contributions over the years have so obviously molded my attitudes toward the treatment of addiction. The support of grants DA-923 and DA-1199 from the National Institute on Drug Abuse is also acknowledged.

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CURRENT STATUS OF NALTREXONE SAFETY DATA

INTERIM REPORT ON CLINIC INTAKE AND SAFETY DATA COLLECTED FROM 17 NIDA-FUNDED NALTREXONE STUDIES

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Oksana Golondzowski, Catharine Dorrier

INTRODUCTION AND BACKGROUND

This article will provide an interim summary of the results of review and analysis of patient intake and safety data collected through February 29, 1976 from 17 NIM-sponsored studies of the narcotic antagonist, naltrexone.

Seven of these studies -- of which most were started in early 1974 under SAODAP grants -- had as one goal the accumulation of data to provide information on the agent's safety. These studies were generally of an open design, although in some, for certain periods or for specific subpopulations, blinding or control group measures were employed.

NIDA additionally contracted the National Academy of Sciences to administer (under the NAS Committee on Clinical Evaluation of Narcotic Antagonists) five other studies of naltrexone in a pilot program to determine the feasibility of double-blind trials of narcotic antagonists in the context of narcotic addiction therapy; these double-blind, placebo-controlled studies, begun in August 1974, were designed to collect data pertinent to the preliminary evaluation of efficacy of naltrexone as well as its safety in treatment of three populations of narcotic addicts.

Although it was not possible to implement the original plan of expanding this program, the five clinics participating were allowed to start new studies using separate protocols and study designs; for purposes of this article these five continuation studies, which "began" in about December 1975, are regarded as separate studies, hence a total of 17 studies reported. The decision to continue these studies

was made in order that the test agent might be allowed to remain available as a treatment option at the participating clinics, and in order to provide sufficient data for the purposes of Phase II safety review by the Food and Drug Administration.

The patient population tested in all 17 studies can be broken down into three major groups -- "street addicts," "methadone maintenance" patients, and "post-addicts," the latter so called because they are known to have been opiate-free for a relatively long period (usually at least six months, often a period of incarceration by the criminal justice system) before entering the present study. The protocols for the five NAS-administered. controlled studies -- which are otherwise substantially identical -- differ to accord with the divergent requirements of these three target populations.

Since the five NAS "continuation" studies began no earlier than December of 1975, the numbers of subjects of these studies for whom safety data are currently available are too small for meaningful inclusion here. Safety data collected for the seven NIDA studies are currently being reviewed and have not been included. This article will therefore present findings with respect to subject intake and retention for all 17 studies, but will present safety data for only five (except for medical terminations in the seven NIDA studies).

PATIENT INTAKE AND RETENTION

Table 1 indicates patient intake data and retention status for the 17 naltrexone studies as of February 29, 1976, the cutoff date for this report. Due to basic differences among the three sets of studies it is inappropriate to make inter-set comparisons on the basis of this table. Figures given for the 10 NAS studies represent subjects assigned to either the active or inactive test medication groups; figures given for the seven safety studies administered directly by NIDA are only for subjects receiving naltrexone.

At the cutoff date, 1,536 patients had been logged in as potential subjects of the 17 studies. Of these, 649 dropped out or were discontinued as study subjects before receiving study medication. A total of 883 had begun receiving study medication, which consisted of placebo in 107 cases among the NAS study subjects. Thus as of that date a total of 776 subjects had had experience of receiving experimental naltrexone treatment.

Of the 883 subjects beginning any study medication, the study participation of 353 subjects had been terminated on or before the 29th day of medication; 275 subjects had been discontinued between one and three months; 154 between three and six months; and the remaining 101 subjects had continued on study medication for over six months.

Retention on study medication

Figure 1 is a graphic representation of subject retention during the course of the study medication periods of the seven NIDA safety studies (naltrexone subjects only) and the five original NAS studies (naltrexone and placebo subjects). (Example: Figure 1 shows that, at the beginning of the fifth month after beginning study medication, approximately 20% of those NIDA study subjects who began naltrexone medication remained in the study.)

In viewing Figure 1, it should be noted that planned medication periods in the NIDA studies ranged from three to 12 months. Thus the reasons for discontinuation of medication of NIDA study subjects between the third and sixth months included program termination in approximately 10 percent of the cases that the curve reflects.

As the figure indicates, retention rates among naltrexone subjects in the five original NAS studies were somewhat higher than those among placebo subjects from the beginning of the sixth week through the end of the 33rd week.

In summary, comparison of these slopes indicates a common relatively rapid attrition over the first two months of study medication; this attrition rate tends to flatten out at about the fourth month. Comparison of the slopes also indicates that -- given the basic differences between the two sets of studies, and especially the differences in scheduled durations of study medication periods -- retention on naltrexone in the NIDA and NAS studies was roughly equivalent.

SAFETY

Terminations for medical reasons

As Table 1 indicates, a total of 883 subjects in all 17 studies had begun study medication as of the February 29 cutoff date. Of the 735 of these subjects whose participation was subsequently terminated before completion of the scheduled medication period, 47 (6.4%) were discontinued for medical reasons, including 34 exhibiting symptoms and/or side effects listed on data form NAS-7 and 13 for whom ab-

TABLE 1

Summary of Clinic Intake and Patient Status
On 17 NIDA-Sponsored Studies Evaluating the Narcotic Antagonist Naltrexone
Data as of February 29, 1976

	NAS CENA Studies	NAS Continuation Studies	NIDA Studies	Total
Number of subjects logged.	735	37	764	1536
Number of subjects whose active study participation was terminated before receipt of initial study medication.	543	1	105	649
Number of subjects who have not yet received any study medication and whose participation has not been terminated.		0	4	4
Number of subjects starting study medication.	192	36	655	883
Number of subjects who received study medication and whose participation was subsequently terminated.	183	16	536	735
a. Refusal to continue taking study medication	19	1	70	90
b. Symptom side effects (NAS-7)	13	3	18	34
c. Abnormal findings on NAS-5A or NAS-5B	4	1	8	13
d. Evidence of readdiction	20	1	33	54
e. Prolonged period(s) of absence	52	6	228	286
f. All other reasons	75	4	179	258
Number of subjects who are currently receiving study medication and whose participation has not been terminated.	9	20	119	148
Duration of Study Medication*				
1 - 29	75	18	260	353
30 - 89	55	13	207	275
90 - 179	31	5	118	154
≥ 180	31	0	70	101
	192	36	655	883

*Study medication - 98 and 9 subjects in the NAS CENA and NAS Continuation Studies respectively received placebo as their study medication. All other subiects received naltrexone.

normal findings were recorded on either the laboratory form, NAS-5A, or the physical/psychiatric form, NAS-5B.

Table 2 indicates the distribution of 45 of these subjects, whether receiving naltrexone or placebo medication, by the clinic's recorded reason for termination and by recorded categorization of the medical abnormality as "possibly drug-related" (PDR), "probably not drug-related" (PNDR), or "unable to determine" (UTD). Complete data on the remaining two of these 47 subjects were not available at the time of this writing.

It will be seen (Table 2) that 39 (5.0%) of the 776 subjects on naltrexone and six (5.6%) of the 107 subjects on placebo medication were discontinued from study participation for medical reasons. The most common reasons for medical terminations were abdominal pains, cramps, or upset stomach (ten naltrexone, no placebo subjects; reported as possibly drug-related in two cases, probably not drug-related in four, unable to determine in four); and withdrawal symptoms (ten naltrexone, two placebo subjects; reported as possibly drug-related in three naltrexone and one placebo case, probably not drug-related in four naltrexone and one placebo case, and unable to determine in the three remaining naltrexone cases). Five naltrexone and one placebo subject were discontinued reportedly due to nervousness or anxiety; this was recorded as probably not drug-related in four naltrexone subjects, and unable to determine in the remaining naltrexone case. Hepatitis was the reported reason for discontinuation of three other naltrexone subjects.

The one remaining naltrexone subject whose symptoms as indicated were "possibly drug-related" developed idiopathic thrombocytopenic purpura . After naltrexone medication was stopped, the symptomatology cleared and platelet count stabilized.

* * * * *

Note: The following sections pertaining to the safety of test medication will present findings only from the original set of five NAS-administered studies, where results for naltrexone can be contrasted directly with those for the placebo controls in those studies. It is anticipated that safety data being collected on subjects receiving naltrexone in the other 12 naltrexone studies will ultimately be contrasted with comparable data on the naltrexone group in this set of NAS studies, to determine the overall consistency of safety findings among all subjects tested with naltrexone.

Abnormal physical/psychiatric findings

Results of regularly scheduled physical and psychiatric examinations were recorded on data form NAS-5B. Findings were reported as "normal" or "abnormal" for each of five items on all subjects: physical examination; EKG; X-ray (chest); psychiatric examination; and neurological examination. A sixth, optional item -- slit lamp examination -- was additionally recorded for 20 subjects.

Table 3 summarizes the findings for each of these items for all study subjects who were "normal" at baseline with respect to the item (or had no recorded baseline evaluation for the item) and who were evaluated for the item at least once during the Study Medication Period. It will be seen that "abnormal" findings resulted from physical, psychiatric, and neurological examinations slightly more frequently among naltrexone subjects than in the placebo group. While statistical analysis of these data is inappropriate, these minor frequency differences do not in themselves appear meaningful; medical review of the individual cases in which abnormal findings were made revealed no problems which placed the safety of naltrexone in question.

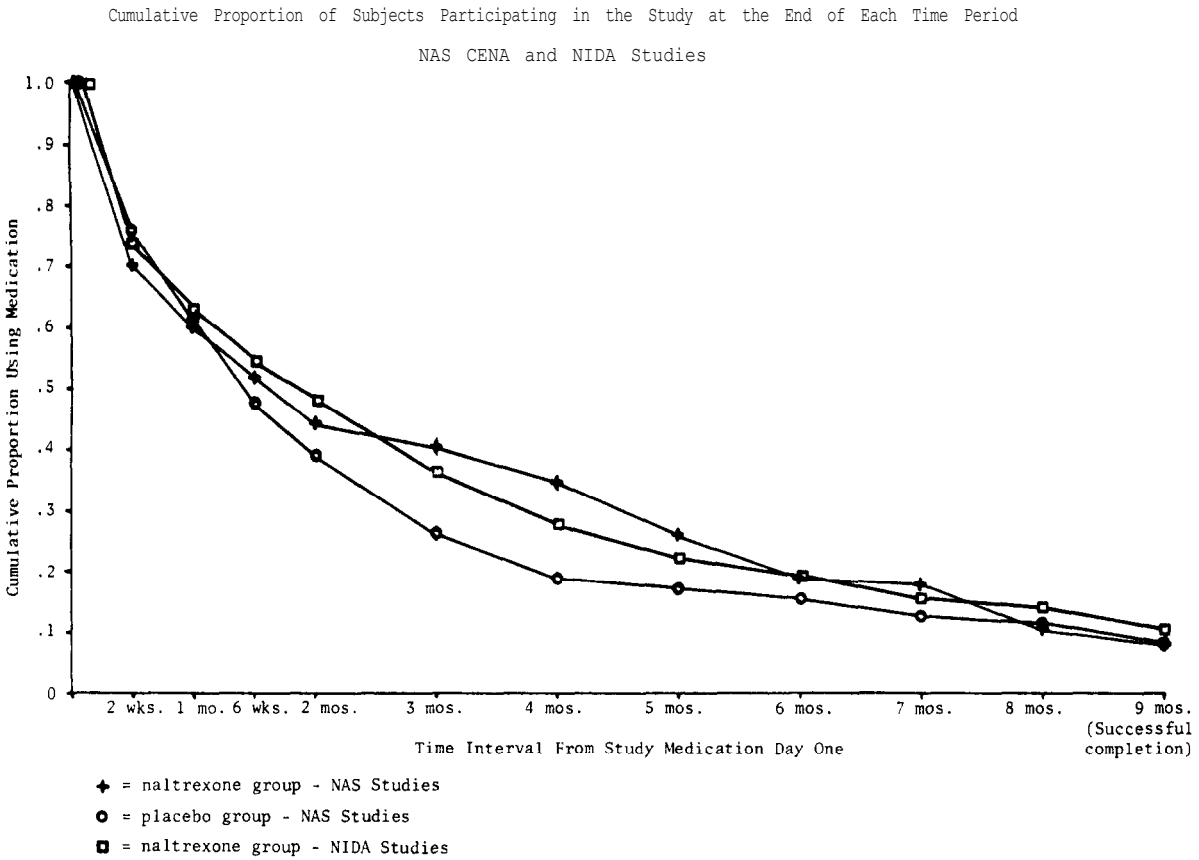
Analysis of laboratory and symptom/side effects data

Three basic approaches were taken in the review and analysis of data pertaining to laboratory findings (form NAS-5A) and to symptoms and side effects (form NAS-7). Since the results of these three approaches constitute the subject of the following sections on safety, this section will describe the three approaches.

The first approach consisted in reviewing in detail data on those subjects who experienced prolonged or pronounced laboratory abnormalities or signs or symptoms. An effort was then made to determine whether these subjects exhibited common problems and to contrast these problems as they occurred among naltrexone- versus inactive-medication subjects within the NAS studies (as noted above, results for the naltrexone group are being compared to results from the other 12 naltrexone studies).

The second approach began with the derivation of frequency counts for the number of times any subjects exhibited abnormal lab values or any signs or symptoms. Two uses were made of these figures. First, they were used to obtain ratios reflecting number of abnormal readings per total number of readings made in the course of study medication per subject. Second, a review was made of all abnormal findings recorded within certain time periods during the period of study medication, to determine whether any abnormalities appeared to be

FIGURE 1



time-specific with regard to onset, duration, or remission.

The third approach employed regression analysis for the detection of any consistent change over time (slope analysis) and of more subtle medication-group differences (analysis of covariance). These are relatively sensitive analyses, which control for recorded baseline status and permit the detection of relatively slight differences between study medication groups and of relatively subtle changes over time within each medication group; the slopes of change for the two groups are then compared to distinguish changes common to both groups from changes specific to one group. The results of analysis using this approach are meaningful only in the context of medical review to determine the clinical significance of the differences and changes detected.

Laboratory data

Twenty-eight required and five optional tests covering hematology, blood chemistry (SMA-12), and urinalysis were run at baseline, at two and four weeks after initiation of study medication, and monthly thereafter during the Study Medication Period. For purposes of indicating "abnormal" values, specific limits (somewhat broader than conventional "normal ranges") were established in advance.

Gross findings: In order to monitor lab safety parameters and to select appropriate subjects for review, twelve specific lab variables were designated as a key set; a review was made of cases in which findings for two or more of these 12 variables were "abnormal." The 12 variables and their predetermined "normal" limits were as follows: total RBC

(4.6-6.2 x 10^6); total WBC (4.5-10.8 x 10^3); hematocrit (40-54 gm%); hemoglobin (13-18 gm%); FBS (60-120 mgm%); BUN (6-23 gm%); alkaline phosphatase (25-85 mU/ml); SGOT (7-50 mU/ml); LDH (90-225 mU/ml); urine albumin (0).

Of the 192 subjects (94 on naltrexone, 98 on placebo) beginning study medication, lab findings for these variables were "abnormal" in at least two instances for 23 naltrexone subjects and 26 placebo subjects. Review of all lab data on these subjects revealed no apparent overall differences between study medication groups. Table 4 indicates the frequency with which these subjects presented three or more "abnormal" readings on any of the lab variables recorded. Frequencies of "abnormal" lab baseline values were generally equivalent for the two medication groups. It is noted that SGOT values during the Study Medication Period exceeded the predetermined upper "normal" limit in nearly half of all cases; statistical analysis of SGOT data -- summarized in Table 5 -- indicated no significant medication-group differences with respect to this variable.

Review was also made of the ratio of all "abnormal" readings to the total number of lab readings recorded during the Study Medication Period; and, for each month during the Study Medication Period, of the ratios of numbers of subjects with "abnormal" readings to total numbers of subjects for whom lab evaluations were made during the month. This review resulted in the following observations:

(1) A slightly higher proportion of naltrexone subjects than of placebo subjects presented abnormal lymphocyte values (generally exceeding the predetermined upper limit);

(2) A slightly higher proportion of naltrexone subjects presented hematocrit values below the predetermined lower limit; and

(3) A slightly higher proportion of placebo

TABLE 2

Summary of 45 Subjects Terminated
from Study Medication for Medically Related Reasons
(Sample Sizes: Naltrexone = 676; Placebo = 107)

	Naltrexone Subject Group			Placebo Subject Group				
	Clinic Impression			Clinic Impression			Total	
Primary Reason Given	PDR	UTD	PNDR	PDR	UTD	PNDR	N	P
General Withdrawal Symptoms	3	3	4	1		1	10	2
Abdominal Pain/Upset Stomach	2	4	4				10	0
Drowsiness, Disorientation/ Insomnia		2	1				3	0
Loss of Appetite, Depression		1				1	1	1
Anxiety, Nervousness		1	4			1	5	1
Reduced Sex Drive		1					1	0
Back Pains		1					1	0
General Illness						1	0	1
Cataract			1				1	0
Hepatitis			3				3	0
Idiopathic Thrombocytopenic Purpura	1						1	0
Recurrence of Kidney Infection		1					1	0
Labile Hypertension		1					1	0
Psychotic Episode			1				1	0
Weight Loss (Withdrawal Symptoms)						1	0	1
Totals	6	15	18	1	0	5	39	6

PDR indicates "Possibly Drug-Related"
UTD indicates "Unable to Determine"
PNDR indicates "Probably Not Drug-Related"

TABLE 3

Summary of All Subjects Whose Baseline Evaluation
Was Not "Abnormal" and Had at Least One
Study Medication Period Evaluation
With Respect o the Physical/Psyhiatric Finding Data

	Total Number of Subjects Meeting Review Criteria		Number and Percentage of Subjects Experiencing One or More "Abnormal" Findings While On Study Medication			
			Number		Percentage	
	N	P	N	P	N	P
Physical Examination	41	40	6	3	14.6	7.5
EKG	46	44	3	5	6.5	11.4
X-ray	41	38	0	0	0.0	0.0
Psychiatric Examination	53	50	2	1	3.8	2.0
Neurological Examination	54	51	1	0	1.9	0.0
Slit Lamp (Optional)	13	7	0	1	---	---

subjects presented fasting blood sugar levels exceeding the predetermined upper limit.

None of these differences was of a degree suggesting significance. With respect to all other lab variables, the numbers and proportions of subjects with "abnormal" readings were approximately equivalent for the two medication groups.

Statistical analysis: Four analyses of covariance adjusting for baseline lab values were run on all subjects for whom lab data were recorded during each of the first three months of study medication; and on all lab data collected during the study on the 23 variables with distributions appropriate for this type of analysis. Of the 92 analyses run, only one -- on albumin (limits: 3.5-5.5 gm%) -- indicated a statistically significant difference between study medication groups, and this occurred only at the third month. Table 5 summarizes the results of all analyses of data pertaining both to albumin and SGOT.

TABLE 4

Gross Finding
Lab Values for Which Any Medication-Group Differences
Was Observed of for Which Both Medication Groups
Exhibited a High Incidence of "Abnormal Values"

(Sample size: naltrexone=23; placebo=26)

Lab Value	Predetermined Limits	Number of Subjects With Three or More Values Outside the Predetermined Limits	
		Naltrexone	Placebo
Lymphocyte	20-45%	6	16
LDH	90-225 mU/ml	7	11
Urine Albumin	0	10	6
SGOT	7-50 mU/ml	16	17
Alkaline Phosphatase	25-85 mU/ml	7	7

To test for more gradual changes over time, and for differences between study medication-group slopes, linear regression models were generated for 20 appropriate lab values. Included in these analyses were data on all subjects for whom laboratory reports were made both at baseline and again during the first and second 45-day periods after starting study medication (32 naltrexone subjects and 35 placebo subjects). Slope estimates which were statistically significantly different from zero resulted in four out of these 40 tests. All four instances occurred in the naltrexone study subject group; these were the slope estimates for hematocrit (slope estimate = 0.22802, $p \leq 0.0162$), uric acid (slope estimate = 0.26293, $p \leq .0051$), and pH (slope estimate = 0.13796, $p \leq .0402$). However, in only two instances were the study medication-group slope estimates significantly different. These are summiarized in Table 6. It is reiterated that the differences resulting from this analysis -- while statistically significant -- are meaningful only in the context of medical review to establish clinical relevance.

TABLE 5

Analysis of Covariance

Summary of Results for Lab Values Having
Any Study Medication-Goup Differences
Or in Which the Group Means Were "Abnormal"

Lab Value & Month		Sample Size		Baseline Means		Unadjusted Means		Adjusted Means		Mean Square Error	P-Value
		N	P	N	P	N	P	N	P		
Albumin	1	53	56	4.58	4.64	4.64	4.60	4.65	4.58	0.14	0.4135
	2	30	34	4.57	4.73	4.69	4.66	4.71	4.64	0.13	0.1676
	3	27	25	4.55	4.65	4.65	4.48	4.67	4.47	0.12	0.0248
	Overall	59	60	4.60	4.67	4.62	4.57	4.63	4.56	0.10	0.1571
SGOT	1	54	57	58.93	63.39	55.84	60.94	57.10	59.74	1571.34	0.8611
	2	31	35	58.06	61.55	57.03	59.40	57.91	58.62	785.57	0.5337
	3	28	27	67.66	72.98	60.03	64.40	60.63	63.78	1044.62	0.9504
	Overall	60	61	61.44	61.49	59.67	64.93	59.68	64.92	1583.03	0.5323

Symptom data

Forms NAS-7, listing 24 possible symptoms (including an "other" category), were completed at baseline and at weekly intervals throughout the Study Medication Period. Specific symptoms were not named by the recorder (i.e., the subject was asked "How were you feeling during the past week?" and, if the subject indicated a particular symptom, he was asked "How bad was that?" and the severity of his response was recorded on a four-point scale.)

Gross findings: A review was made of those cases in which the most frequent and/or severe symptoms were recorded; these cases included 12 naltrexone subjects and five placebo subjects. Additionally, a review was made of all

cases with symptoms marked other than "none" both for overall incidence and for over time changes based on biweekly review points. Those symptoms most nearly suggestive of a difference between medication groups -- occurring with greater frequency in the naltrexone group -- tended to refer to the gastrointestinal system, e.g. "abdominal pain or cramps" and "nausea or vomiting."

Statistical analysis: At least four weekly symptom forms (NAS-7) were collected for 58 naltrexone subjects and 49-51 (depending on symptom) placebo subjects. Data on these subjects were analyzed using simple 2x2 χ^2 tests in order to detect statistical differences between medication groups with respect to simple incidence of "other than 'none"' recordings both in the first 60 days of study medication and over the course of the Study Medication Period.

TABLE 6

Summary of the Two Lab Values in Which Statistically Significant Findings Resulted

	Slope Estimates and P-Values For Both Study Medication Groups				Common Slope Estimate and P-Value		F-Test Statistic For Slope Equivalence	Resultant P-Value (P<)
	Naltrexone (n=32)		Placebo (n=35)		Combined			
	Slope	P(β=0)	Slope	P(β=0)	Slope	P(β=0)		
Bilirubin	0.04397	0.0951	-0.03139	0.2421	0.00316	0.8673	4.04817	P<0.05
pH	0.13796	0.0402	-0.06157	0.3857	0.03228	0.5120	4.22035	P<0.05

The incidence of subjects for whom any symptom recordings of other than "none" were made was less than 10% on ten of the 24 items recorded, including "Increased Thirst," "'High' Feeling," "Increased Energy," "Speeding," "Numb Feeling," "Difficulty Concentrating," "Delayed Ejaculation," "Decreased Potency," "Dizziness," and "Skin Rash." With respect to ten additional items -- "Diarrhea," "Feeling Down," "Low Energy/Fatigue," "Difficulty Sleeping," "Anxiety/Nervousness," "Irritability," "Headache," "Chills," "Joint/Muscle or Back Pains" and "Other" -- the medication groups were not statistically differentiable in either the 60-day or overall test.

The naltrexone group experienced a greater incidence of the remaining four items; the study medication-group difference was statistically significant, or approached significance, in each instance. Table 7 summarizes the results of analysis of data pertaining to these four symptoms.

Summary

In 17 studies of naltrexone, a total of 1,536 patients had been logged in as potential study subjects as of February 29, 1976. Of these, 883 had been started on study medication, including 107 on placebo as controls. A relatively high rate of attrition was seen in all studies over the first two months of study medication; this attrition rate tended to flatten out at about the fourth month.

Of the 883 subjects beginning study medication, 47 (5.3%) were subsequently terminated for medical reasons. The data available on 4.5 of these subjects indicate equivalent percentages, both with respect to the total number of dropouts in the two study medication groups (naltrexone: 39 of 676, or 5.0%; placebo: 6 of 107, or 5.6%) and to the number of dropouts which the clinic reported as "possibly drug-related" (naltrexone: 6 out of 676, or 0.9%; placebo: 1 of 107, or 0.9%). However, one of the "possibly drug-related" dropouts developed idiopathic thrombocytopenic purpura after the administration of naltrexone for approximately 13 months during four separate treatment admissions.

Statistical review of the data and subsequent analyses of the five double-blind, placebo-controlled studies administered by the National Academy of Sciences revealed no significant medication-group differences with respect to the physical/psychiatric or laboratory data. A review of the symptom data and analyses indicates that the frequency of occurrences of certain of the gastrointestinal tract symptoms recorded was somewhat higher in those subjects treated with naltrexone. Specific symptoms involved included "Loss of Appetite," "Abdominal Pain or Cramps," "Nausea or Vomiting," and "Constipation." However, the relative severity of these symptoms for all subjects experiencing any symptomatology was not statistically differentiable with respect to study medication group.

TABLE 7

Subject Distribution of Average Symptom Severity Score During First 60 Days of Study Medication and Overall with Summary of 2 x 2 X^2 Analysis of Symptom Incidence Includes All Subjects Having At Least Four Readings

Symptom	Study Medication Period	Medication	Symptom Severity Interval: None	.01-.25	.26-.50	.51-.75	.76-1.00	1.01-2.00	2.01-3.00	Subj. Total	X^2 P-Value ($p \leq$)
Loss of Appetite	First 60 Days	N	47	3	3	1	3		1	58	.094
		P	46		3					49	
	Overall	N	43	9	4		1	1		58	.026
		P	47	2	2					51	
Abdominal Pain or Cramps	First 60 Days	N	41		8	3	2	4		58	.405
		P	39	3	2	2	1	2		49	
	Overall	N	33	12	7	1	4	1		58	.085
		P	38	6	4	1		1	1	51	
Nausea or Vomiting	First 60 Days	N	44	4	7	2	1			58	.052
		P	45	1	3					49	
	Overall	N	36	14	7	1				58	.059
		P	41	7	2	1				51	
Constipation	First 60 Days	N	48	2	3	2	1	2		58	.024
		P	48		1					49	
	Overall	N	47	6	1	1	1	2		58	.442
		P	45	4	2					51	

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- Agenda -

Satellite Conference on Naltrexone

In Conjunction with the
38th Annual Scientific Meeting
Committee on Problems of Drug
Dependence

Richmond Hyatt House
Richmond, Virginia
June 6 & 7, 1976

Time	Topic or Title	Speaker
SUNDAY JUNE 6 (8:30-10:30 a.m.)	SESSION I: Naltrexone - Current Status of Federal Research and FDA Regulations	CHAIRMAN: Demetrios A. Julius, M.D.
8:30-9:00	NIDA's Naltrexone Research Program	Demetrios A. Julius, M.D.
9:00-9:20	Requirements for Drug Development	Edward C. Tocus, Ph.D.
9:20-9:40	Preclinical Toxicity Studies of Naltrexone	Monique Braude, Ph.D.
9:40-10:00	The Effects of Naltrexone in the Chronic Spinal Dog and Acute Spinal Cat; Possible Interaction with Naturally-occurring Morphine-like Agonists	William Martin, M.D.
10:00-10:20	The Development of Sustained Action Preparations of Narcotic Antagonists	Robert E. Willette, Ph.D.
10:20-10:30	Open Discussion	
10:30-10:50	BREAK (Coffee)	
(10:50-12:30 p.m.)	SESSION II: The NAS CENA Studies	CO-CHAIRMEN: Alex Bradford, M.S. Walter Ling, M.D.
10:50-11:10	Evolution of the National Academy of Sciences Study of Naltrexone	Samuel Kaim, M.D.
11:10-11:30	Philosophy and Status of the NAS CENA Studies	Leo Hollister, M.D.
11:30-11:50	Varying Clinical Contexts for Administering Naltrexone	Marc Hurzeler, M.D.
11:50-12:10	Patient Response to Naltrexone: Issues of Acceptance, Treatment Effects, and Frequency of Administration	Stephen Curran, M.A.

Time	Topic or Title	Speaker
12:10-12:30	Open Discussion	
12:30-2:05	BREAK	
(2:05-3:35 p.m.)	SESSION III: The NAS CENA Studies (Continued)	CHAIRMAN: Walter Ling, M.D.
2:05-2:25	Naltrexone in Methadone Maintenance Patients Electing to Become 'Drug Free'	Neil Haas, M.D.
2:25-2:45	Comments and Findings from a Naltrexone Double Blind Study	John Keegan, M.A.
2:45-3:05	Factors Influencing Success in an Antagonist Treatment Program	James Crawford, M.A.
3:05-3:15	Open Discussion	
3:15-3:35	BREAK (Coffee)	
(3:35-5:15 p.m.)	SESSION IV: The NIDA Clinical Studies	CO-CHAIRMEN Demetrios A. Julius, M.D. Alex Bradford, M.S.
3:35-3:55	Clinical Experience with Naltrexone in 370 Detoxified Addicts	Muriel Thomas, R.N.
3:55-4:15	Narcotic Antagonist Treatment of the Criminal Justice Patient- Institutional vs. Outpatient - Including a 24-Hour Detox Naltrexone Induction Regimen with Oral Medication	Leonard Brahen, M.D.
4:15-4:35	Use of Narcotic Antagonists (Naltrexone) in an Addiction Treatment Program	David Lewis, M.D.
4:35-4:55	An Analysis of Naltrexone Use--Its Efficacy, Safety and Potential	Ralph Landsberg, D.O.
4:55-5:15	Open Discussion	
	BREAK	
(7:30-10:00 p.m.)	SESSION V: Current Assessment of Naltrexone's Safety	CO-CHAIRMEN: Walter Ling, M.D. Alex Bradford, M.S.
7:30-9:00	Interim Report on Clinic Intake and Safety Data Collected from 17 NIDA-Funded Naltrexone Studies	Alex Bradford, M.S.
9:00-10:00	Open Discussion: Is Naltrexone Safe for Use in Heroin Addicts	

Time	Topic or Title	Speaker
MONDAY JUNE 7 (7:00-10:30 p.m.)	SESSION VI: The NIDA Behavioral Studies	CHAIRMAN: Abraham Wikler, M.D.
7:00-7:20	The Theoretical Basis of Narcotic Addiction Treatment with Narcotic Antagonists	Abraham Wikler, M.D.
7:20-7:40	Limitations of an Extinction Approach to Narcotic Antagonist Treatment	Roger E. Meyer, M.D.
7:40-8:00	Naltrexone in a Behavioral Treatment Program	Charles O'Brien, M.D.
8:00-8:20	Comparison of Two Naltrexone Treatment Programs: Naltrexone Alone Versus Naltrexone plus Behavior Therapy	Edward J. Callahan, Ph.D.
8:20-8:30	BREAK (Coffee)	
8:30-10:30 p.m.)	SESSION VII: The Use of Naltrexone in Treatment of Heroin Addiction	CO-CHAIRMEN: Walter Ling, M.D. Alex Bradford, M.S.
8:30-8:50	Naltrexone in the Management of Heroin Addiction: Critique of the Rationale	Avram Goldstein, M.D.
8:50-9:10	Clinical Experience with Naltrexone in a Behavioral Research Study	Robert Greenstein, M.D.
9:10-9:30	Clinical Efficacy of Naltrexone: A One Year Follow-Up	Richard Resnick, M.D.
9:30-10:30	Open Discussion: Use of Naltrexone in Treatment of Heroin Addiction	

The current naltrexone research program has been supported by the National Institute on Drug Abuse under the following contracts and grants.

Samuel C. Kaim, M.D.	SAODAP Contract DA 3AC694 NIDA Contract 271-76-3301
Marc Hurzeler, M.D.	NIDA Contract HSM-42-72-3301
Neil Haas, M.D. Walter Ling, M.D.	SAODAP Grant DA 4PG 023
Kenneth Schoof, M.D. John Keegan, M.A.	NIDA Contract HSM 42-73-255
Sadashiv Parwatikar, M.D.	NIDA Contract HSM 42-72-116
Richard B. Resnick, M.D.	NIDA Contract HSM 42-73-258
Leonard Brahen, Ph.D., M.D.	NIDA Contract HSM 42-72-210 NIDA Grant DA 01259
David Lewis, M.D.	NIDA Contract HSM 42-73-264
Ralph Landsberg, D.O.	NIDA Contract HSM 42-73-259
Charles Savage, M.D. Stephen Curran, M.A.	NIDA Grant DA 00415
Roger E. Meyer, M.D.	NIDA Grant DA 00257
Charles P. O'Brien, M.D., Ph.D. Robert Greenstein, M.D.	NIDA Contract HSM 42-73-225 NIDA Grant DA 01218
Alex Bradford, M.S.	NIDA Contract 271-75-3050

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