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Clonidine and naltrexone: rapid treatment of opioid withdrawal in the outpatient setting

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RAPID TREATMENT OF OPIOID WITHDRAWAL
IN THE OUTPATIENT SETTING

EUGENIA MARIE VINING
1987
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March 30, 1987
(Date)
Clonidine and Naltrexone:
Rapid Treatment of Opioid Withdrawal
in the Outpatient Setting

A Thesis Submitted to the Department of Psychiatry
Yale University School of Medicine
in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Medicine

by

Eugenia Marie Vining
1987
For Bob
and
For My Parents
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have taught me much more than I could have ever learned elsewhere.
ABSTRACT

Clonidine and Naltrexone:
Rapid Treatment of Opioid Withdrawal in the Outpatient Setting

Eugenia Marie Vining
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Clonidine hydrochloride (an alpha-2 adrenergic agonist) and naltrexone hydrochloride (an opioid antagonist), given in combination, provide a safe and effective treatment of abrupt opioid withdrawal over 4 or 5 days in an outpatient/day setting. Following a naloxone challenge test to verify and quantify opioid dependence, fourteen of 17 (82%) heroin users successfully withdrew from opioids and attained maintenance levels of naltrexone. Eight of 9 (89%) successfully completed the 5 day study in which naltrexone therapy was begun on day 2. Six of 8 (75%) successfully completed the 4 day study in which naltrexone therapy was begun on day 1. Three to 5 days of clonidine hydrochloride treatment with a peak mean dose of 0.6 mg/day on day 2 for the patients in the 5 day study, and 0.5 mg on days 1 and 2 for patients in the 4 day study, attenuated the withdrawal inducing effects of naltrexone. Both groups received naltrexone in single morning doses which were rapidly increased from 12.5 mg on the first day of naltrexone therapy to 50 mg on the third day. Significant correlations were observed between naloxone challenge test score and
observer-rated symptomatology during treatment. Clonidine significantly decreased blood pressure in both groups without producing clinical problems. This study has improved the availability of the clonidine-naltrexone combination by developing a single dose per day naltrexone regimen with naltrexone doses generally available to any opioid treatment facility.
INTRODUCTION

The last of the codeine was running out. My nose and eyes began to run, sweat soaked through my clothes. Hot and cold flashes hit me as though a furnace door was swinging open and shut. My legs ached and twiched so that any position was intolerable, and I moved from one side to the other, sloshing about in my sweaty clothes.

William S. Burroughs, *Junky* 1953

Opioid withdrawal, so vividly described by William S. Burroughs in his powerful account of heroin addiction, is a syndrome of autonomic disturbance and psychic distress which drives the addict to continued opioid use. This abstinence syndrome as well as tolerance to the effects of increasing amounts of opioids characterize opioid dependence (APA, 1980). Successful treatment of opioid dependence involves treatment of the withdrawal syndrome and assistance afterward so that the former addict can remain drug-free.

At the turn of the century, treatment of narcotic addiction was often considered synonymous with successful withdrawal. New treatments were advanced periodically and then discarded as ineffective and often harmful. Sodium thiocyanate, lipids, sodium bromide, insulin and other hormones were just some of the agents used to "treat" opioid withdrawal (Kleber, 1982). One of the most popular methods of detoxification at this time employed belladonna agents (Kolb and Himmelsbach, 1938). Scopolomine was administered every 30 to 60 minutes over a one to two day period. During this detoxification patients would hallucinate and become wildly delirious, symptomatic of belladonna toxicity. Fortunately, such treatments were denounced as more distressing and harmful to
addicts than withdrawal itself; however, this was not until a number of deaths had already resulted from them.

In their review article criticizing many of these forms of treatment, Kolb and Himmelsbach proposed a "rapid withdrawal" method of detoxification in which doses of morphine and codeine would be gradually tapered over a seven day period (Kolb and Himmelsbach, 1938). This method of detoxification would dominate treatment modalities until the discovery of methadone during the Second World War (Isbell et al, 1947). In addition, citing faulty observation of the course of withdrawal as the cause for failure of previous "treatments," these investigators outlined a quantitative method for measuring abstinence syndrome intensity. This method enabled objective evaluation of future treatment modalities and became the model for present day abstinence rating scales.

Methadone was synthesized by the Germans during World War II, and soon underwent intensive clinical investigation in the United States (Isbell et al, 1947; Isbell et al, 1948). These studies revealed that methadone was an addictive substance that produced an abstinence syndrome with milder, more prolonged symptoms than morphine or heroin (Isbell et al, 1948). Investigators also found that methadone could prevent the abstinence syndrome in morphine dependent patients (Isbell et al, 1948). Researchers quickly realized the advantages of this cross tolerance. Placing morphine or heroin dependent patients on methadone would substitute the more intense abstinence syndrome produced by these short-acting opiates with the much milder withdrawal from methadone. Soon methadone was being used as an agent for detoxifying opioid addicts (Isbell and
Vogel, 1949). In these initial studies, methadone would be substituted for the opioid of abuse, and gradually tapered over a 7 to 10 day period (Isbell and Vogel, 1949).

Since the work of Isbell and Vogel in 1949, investigators have conducted many studies examining the efficacy of both inpatient and outpatient methadone detoxification. In their study comparing the cost and effectiveness of hospital versus outpatient detoxification, Wilson and his colleagues reviewed previous detoxification studies using methadone (Wilson et al, 1975). In these studies, methadone was administered over time periods ranging from 2 weeks to 11 months on both an inpatient and outpatient basis. Only 3% to 25% of patients were able to successfully complete detoxification. Follow-up of those patients further demonstrated that only 7% to 19% of patients who had been successfully withdrawn remained drug-free 6 months after treatment (Wilson et al, 1975).

Wilson's own study used a 10 day methadone regimen to detoxify 40 heroin addicts, 10 in the hospital, and 30 in an outpatient setting (Wilson et al, 1975). One inpatient (10%) and 6 outpatients (20%) completed the detoxification. No inpatients (0%) and only 2 outpatients (7%) remained drug-free 2 months after the detoxification was complete. The authors concluded that there was little benefit from either treatment approach, but that outpatient therapy was no less successful than inpatient. Outpatient trials employing 7 day and 90 day protocols demonstrated successful detoxification rates of 32% and 13%, respectively (Silsby and Tennant, 1974; Wilson et al, 1974). Six months following the
detoxification, 9.5% of those from the 7 day study and none of those from the 90 day study were drug-free.

Senay, Dorus, and Showalter examined the 21 day methadone detoxification recommended by the Food and Drug Administration and compared it to an 84 day methadone detoxification under double-blind conditions (Senay et al, 1981). They found that 4 of 32 (13%) patients completed the 21 day detoxification; however, none of these patients completed the full 90 day protocol. Five of 36 (14%) patients completed the 84 day detoxification and went on to complete the full 90 day protocol. All of these patients had remained drug-free in the follow-up period of 12 months or less (mean = 4.1 months). They concluded that although the percentage of patients remaining drug-free was not large in either group, the more gradual 84 day schedule increased the probability that patients would remain in treatment, without increasing their chances of becoming severely dependent on methadone (Senay et al, 1981).

The concern that short term management of opioid withdrawal with methadone might lead to long term dependence on this agent was not unfounded. Methadone maintenance programs were initially established to ensure a "stable addiction" for patients, obviating the need for heroin as well as the criminal activity often necessary to support heroin use (Dole and Nyswander, 1967; Bowden and Maddux, 1972). Orally administered methadone at a certain dose level does not appear to have a euphoric effect, but induces a marked, slowly developing tolerance to all opiate-like drugs, including methadone itself (Jaffe and Martin, 1985). As a result, the patient cannot feel the euphoric effect of ordinary doses of other narcotics such as
heroin or morphine. Methadone maintenance stabilizes the patient's a physiologic dependence, affording him the opportunity to modify his life in other areas: to achieve some stability in his family and other interpersonal relationships and to move away from involvement with heroin users and the subculture such use engenders. Although methadone maintenance has achieved a certain amount of success in moving the addict toward socially productive behavior, it has problems associated with its use (Szara and Bunney, 1981). Because it is an opioid agonist with addictive potential, diversion to illegal channels is one of these problems. In addition, once on methadone maintenance, it has been difficult for the patient to achieve abstinence from methadone, an important goal of treatment.

Kleber's review of studies examining detoxification from methadone maintenance demonstrates varying success rates (Kleber, 1977). Successful detoxification of those felt "appropriate for detoxification," that is, those in good standing who were not being discharged from the program, ranged from 8% to 53% (Kleber, 1977). Relapse even after successful detoxification was considerable with only 20% to 33% of patients drug-free in a follow-up period of less than two years. One study has demonstrated quite successful withdrawal and follow-up statistics. Riordan and colleagues reported on 59 patients on methadone maintenance who were in good standing and underwent voluntary withdrawal (Riordan et al, 1976). Of this group, 49 (84%) successfully completed detoxification. Of the 38 individuals followed-up at time periods ranging from 6 to 44 months after detoxification, 26 (68%) had remained drug-free.
Despite these more optimistic results, investigators have continued to search for methods of detoxification that were more rapid and effective than methadone, without using opioid agonists or other addictive substances. Their efforts were facilitated by discoveries leading to a better understanding of the neuropharmacology of opioid dependence and withdrawal. Chronic administration of opioids produces profound effects on endogenous opioid function and noradrenergic activity in the central nervous system (Korf et al, 1974; Hollt et al, 1978; Herz et al, 1978; Przelocki et al, 1979). Although long term opioid administration does not appear to alter enkephalin levels, it does decrease endorphin synthesis as well as functional sensitivity to opioid agonists (Herz et al, 1978; Przelocki et al, 1979). In addition, studies of the brain's major noradrenergic nucleus, the locus coeruleus (LC), demonstrated that the prototype opiate morphine causes a marked reduction in LC neuronal firing rate (Korf et al, 1974). This decrease in LC activity and norepinephrine release is followed by a reciprocal increase in alpha-2 and beta adrenergic receptors in areas receiving LC projections (Llorens et al, 1978; Hamburg and Tallman, 1981). These data suggest an important role for the LC in opioid dependence withdrawal: some of the effects of opioids might be mediated through a decrease in LC activity and noradrenergic release. The discovery of specific opioid receptors in the brain (Hughes, 1975), with a high concentration located in the LC (Pert et al, 1975) was further evidence supporting such a mechanism.

Studies in rodents and primates provided additional data implicating the neurotransmitter norepinephrine in opioid
dependence and withdrawal (Redmond, 1977; Cedarbaum and Aghajanian, 1977; Svensson et al, 1975; Meyer and Sparber, 1976). Gunne had previously shown that total brain norepinephrine decreased during opioid withdrawal suggesting that withdrawal was associated with increased norepinephrine release (Gunne, 1959). Cedarbaum and his colleagues found that an intravenous dose of the alpha-2 adrenergic agonist clonidine inhibited the spontaneous firing of brain norepinephrine-containing neurons in the LC by acting directly on the noradrenergic receptors located on those neurons (Cedarbaum and Aghajanian, 1977). Based on this knowledge clinicians have tried to modify opioid euphoria and withdrawal by giving drugs which modify these neurotransmitters. The beta adrenergic antagonist propranolol (Grosz, 1972), alpha adrenergic antagonists (Davis and Smith, 1973), and noradrenergic synthesis inhibitors (Davis and Smith, 1973) all have effects on opioid withdrawal. None of these agents has been shown to be as effective in alleviating the discomfort of withdrawal as the alpha-2 adrenergic agonist clonidine.

In 1978, Clonidine hydrochloride was used by Gold to successfully block acute opiate withdrawal symptoms in 11 patients abruptly withdrawn from methadone maintenance (Gold et al, 1978a). Patients were given clonidine 36 hours after their last methadone dose (range = 15-50 mg methadone), when they all had objective signs of opioid withdrawal. All patients experienced relief of abstinence signs and symptoms for 4 to 6 hours after receiving a 5 μg per kg dose of clonidine. In a subsequent study, clonidine enabled 10 of 10 (100%) patients to successfully withdraw from
methadone (Gold et al, 1978b). This technique permitted patients to detoxify from methadone in less than 2 weeks with fewer symptoms than they would experience during the usual 4-6 month methadone detoxification.

It was soon after this clinical success that Aghajanian, using single neuronal recording techniques and microiontophoresis, reported his investigation of the mechanism of clonidine as well as of the role of the LC in opioid withdrawal (Aghajanian, 1978). He found that endogenous and exogenous opioids decrease LC firing rates and that the opioid antagonist naloxone reversed this suppression of the LC. He observed that chronic opioid administration produced tolerance of the LC neurons to opioid suppression. Naloxone precipitated withdrawal produced the predicted noradrenergic hyperactivity which was reversible with clonidine. Furthermore, naloxone administration overrode morphine's suppression of the LC, but was unable to override clonidine's suppression of LC firing. He concluded that the LC is under the dual control of opioid and alpha-2 adrenergic receptors. Opioid withdrawal produces central noradrenergic hyperactivity through disinhibition of the LC. This noradrenergic hyperactivity can be blocked by the alpha-2 adrenergic agonist clonidine through its action at receptors distinct from the opioid receptors to which morphine binds.

Subsequent studies have demonstrated that clonidine does not alleviate withdrawal solely through its inhibition of noradrenergic firing. Lesions of noradrenergic neurons do not reduce clonidine's ability to attenuate behavioral signs of withdrawal (Britton et al, 1984). The amygdala (Freedman and Aghajanian, 1986), spinal cord
(Franz et al, 1982), and forebrain (Matsui and Yamamoto, 1984) have all been proposed as other areas of clonidine's activity in opiate withdrawal.

Since the initial studies by Gold (Gold et al, 1978a; Gold et al, 1978b, Gold et al, 1980), other investigators have demonstrated clonidine's ability to ameliorate the abstinence syndrome in patients previously maintained on methadone with success rates of 80% to 90% (Uhde et al, 1980; Kleber et al, 1980; Charney et al, 1981). In double blind, placebo controlled studies, clonidine has proven itself more effective than placebo (Gold et al, 1978b) and as effective as a 20 day methadone taper (Kleber et al, 1985; Washton and Resnick, 1981) in alleviating the signs and symptoms of methadone withdrawal. Although it was recommended that shorter acting narcotics be withdrawn in less than a week using clonidine (Kleber et al., 1980), no inpatient studies and very few outpatient studies had examined clonidine's efficacy in detoxification from these agents.

Early attempts at outpatient detoxification using clonidine were less successful. In the first double-blind study comparing clonidine and methadone in an outpatient setting, 31% of patients receiving clonidine were successfully detoxified from methadone maintenance compared to the 46% of patients undergoing rapid methadone taper (Washton and Resnick, 1980). In a subsequent study by the same investigators, 31 of 39 (80%) methadone patients and 4 of 11 (36%) heroin users were successfully detoxified using clonidine, for an overall success rate of 70% (Washton and Resnick, 1980). In this same study, a sub-group of methadone patients was detoxified using clonidine in conjunction with gradual methadone dose reductions.
Ten of 20 (50%) patients were successfully withdrawn in this manner. Kleber and colleagues also assessed clonidine detoxification under double-blind conditions (Kleber et al, 1985). Of 49 methadone patients whose dose had been lowered to 20 mg, 25 were detoxified using methadone tapered at 1 mg decrements, and 24 by abrupt substitution with clonidine. They found that 9 of 23 (39%) in the methadone group and 10 of 24 (42%) in the clonidine group achieved successful detoxification, with one third of the patients successfully detoxified in both groups maintaining abstinence over the subsequent six months. These success rates of outpatient clonidine detoxification contrasted sharply with the 80% to 90% success rate of clonidine inpatient detoxification.

Outpatient detoxification using clonidine involves difficulties that do not arise in an inpatient trial. First, potential clonidine side effects such as hypotension and sedation are more difficult to managed on an outpatient basis. In an inpatient setting, increased clonidine doses can be used because of the increased capacity to monitor side effects. For this reason, clonidine doses given to outpatients at Yale have been tapered or held if diastolic blood pressure dropped below 55, or systolic pressures were lower than 85. Second, the temptation and opportunity to deal with discomfort by using narcotics is greater in outpatient settings where these agents are more readily available. However, despite these drawbacks of outpatient detoxification, there are compelling reasons for improving the efficacy of outpatient therapy: many patients are unable to be hospitalized for the time required by inpatient programs; many programs do not have an inpatient detoxification
unit available; finally, inpatient treatment places more stress on limited medical resources.

In addition to the problem of lower success rates in the outpatient setting, both clonidine and methadone therapy failed to shorten the time required for withdrawal. This was especially problematic in the outpatient setting, for a long duration of mild withdrawal symptoms affords outpatients a greater opportunity to resume opioid use. Previous efforts to shorten the withdrawal period by Blachley and his colleagues demonstrated that the pure opiate antagonist naloxone given parenterally to opiate dependent patients precipitated withdrawal and shortened the period required for this withdrawal (Blachley et al, 1975). They noted that the intensity of this precipitated withdrawal decreased with successive doses of naloxone with the withdrawal period complete in 1 or 2 days. Despite their claims that patients experienced less total discomfort than that experienced with longer, but more gradual withdrawal, this means of detoxification was never practiced extensively. Other groups have tried this technique (Kurland and McCabe, 1976; Resnick et al, 1977), but were never able to satisfactorily ameliorate the intensified withdrawal symptoms with symptomatic medication.

Based on data that clonidine had been noted to block naloxone induced morphine withdrawal (Meyer and Sparber, 1976), Riordan and Kleber combined clonidine and naloxone therapy to successfully withdraw 3 heroin users and 1 methadone patient over a 4 day period. This was accomplished in a three stage procedure. On day 1, opioids were withheld and patients received only clonidine; on days 2 and 3, patients received both clonidine and naloxone; on day 4,
patients received clonidine and a single evening dose of naloxone to
determine whether they had any persistent opioid tolerance (Riordan
and Kleber, 1980). All 4 (100%) inpatients were successfully
detoxified using this method.

Naloxone (N-allylnoroxymorphone) is a pure opiate antagonist
effective only when administered parenterally (Eddy and May,
1973). Although naloxone produces effective blockade of morphine,
this blockade is short lasting and decays completely over a 4 hour
period. One study has demonstrated naloxone's ability to attain
effective blockade of morphine for nearly 24 hours; however, this
required 3,000 mg per day of naloxone, a dangerously large dose of
this agent (Zaks et al, 1971). This short half-life and parenteral route
of administration severely limited the use of naloxone in the
treatment of opioid dependency.

In 1965, Blumberg and Dayton synthesized naltrexone (N-
cyclopropyl-methylnoroxymorphone), an analogue of naloxone which
was longer lasting and potent orally (Blumberg and Dayton, 1972).
The principal pharmacologic action of naltrexone is that of an opioid
antagonist. Naltrexone blocks the action of opioids by competitive
binding at the opioid receptor to displace any opioids present as well
as block the effects of subsequent opioid administration. To avoid
the precipitation of the opioid abstinence syndrome, it is
recommended that patients using short-acting opioids, such as heroin
and morphine, await 7 days after their last use of that substance
before initiating naltrexone therapy (Kleber et al, 1985a).
Individuals using longer-acting opioids, such as methadone, are
advised to wait 10 days before initiating naltrexone therapy.
However, the longer the interval before naltrexone is begun, the greater the chance that the addict will return to opioid use. Because of this, investigators have continued to search for treatment modalities which would both shorten the withdrawal syndrome as well as enable earlier naltrexone induction.

Charney and his colleagues used clonidine and naltrexone in combination to provide a safe, effective, and rapid withdrawal for patients maintained on methadone (Charney, 1982). Over a 6 day period, 10 of 11 (91%) patients were able to withdraw completely from methadone therapy. This detoxification was also accomplished in two stages. On day 1, patients had their regular methadone maintenance dose held and received clonidine therapy alone. On days 2 and 6, patients received oral naltrexone therapy in addition to clonidine. The naltrexone was administered in increasingly higher doses until day 5 when maintenance levels (50 mg) were attained in a single daily dose. Clonidine doses had reached a maximum on days 2 and 3 (2.9 +/- 0.6 and 2.3 +/- 0.6, respectively) and were rapidly tapered on days 4 through 6. No one required clonidine therapy after day 6. Three of the 10 (30%) patients decided to continue on naltrexone maintenance therapy. In a follow-up period ranging from 4 months to one year, only 1 of the 10 patients had returned to opioid use. In an extension of this study, Charney examined a total of 40 methadone patients who were detoxified using combination clonidine and naltrexone therapy (Charney et al, 1986). Fourteen (including the 11 from the previous study) were detoxified using the same two stage dosage regimen described above. Twenty-six were detoxified in a single stage procedure, eliminating
the first day of clonidine therapy alone. Patients in this group received both clonidine and naltrexone therapy on days 1 through 4 of the study and attained naltrexone maintenance levels (50 mg) by day 4. For both groups, naltrexone doses were gradually increased from 1 mg to 50 mg over a 4 day period. Thirty-eight of 40 (95%) patients withdrew from opioids completely over the 4 or 5 day period.

Combination clonidine and naltrexone therapy has also been proven effective in the outpatient setting. Over a 5 day period Kleber and colleagues successfully withdrew 12 of 14 (86%) heroin users from opioids while simultaneously initiating naltrexone therapy (Kleber et al, in press). This study was conducted using clonidine and naltrexone doses similar to those used in the previous inpatient study (Charney et al, 1982; Charney et al, 1986). An important difference was a naloxone challenge test (NCT) administered on the first day of the study. Unlike the patients in Charney's study who had been maintained on a known amount of methadone, patients in this study used illicit opiate preparations with inconstant opiate concentrations. The naloxone challenge test was used to establish opioid dependence in these patients as well as objectively quantify that dependence (Wang, 1974; Weisen; 1977; Wang 1982). This ensured that only opioid dependent individuals entered the detoxification, and that those who did received adequate initial clonidine doses. Of the 12 patients who successfully completed the 5 day detoxification and the week of naltrexone maintenance, 5 (42%) remained in naltrexone maintenance one month later and 3 others (25%) claimed to be completely drug free.
These studies demonstrate that combination clonidine and naltrexone therapy is able to speed the time course of opiate withdrawal without increasing symptomology (Charney et al, 1982; Charney et al, 1986; Kleber et al, in press). In addition, naltrexone and clonidine detoxification appears to equalize the time course of the heroin and methadone withdrawal syndromes (Kleber, in press). Naltrexone is thought to speed the process of withdrawal by rapidly reversing opioid-induced central noradrenergic hypersensitivity. Administration of naltrexone to opioid dependent animals rapidly reverses morphine-induced increases in the number of brain alpha-2 and beta adrenergic binding sites (Hamburg and Tallman, 1981; Cedarbaum and Aghajanian, 1977). Clonidine is able to suppress the intensified noradrenergic discharge which naltrexone would otherwise produce, and in this manner alleviate withdrawal symptomatology. The clonidine naltrexone protocol appears to equalize the heroin and methadone withdrawal syndromes by displacing opioids from binding sites thereby eliminating the effects of opioid half-life on the time course of central noradrenergic normalization (Kleber in press).

Outpatient clonidine and naltrexone detoxification is a safe and effective method of treating opiate withdrawal. This therapeutic combination also facilitates follow-up naltrexone maintenance therapy, effective treatment for the relapsing character of opioid dependence. Failure of previous outpatient clonidine detoxifications to match inpatient success rates may have been due largely to the greater temptation and opportunity to deal with discomfort by using opioids which are more available in the outpatient setting. The
addition of naltrexone therapy removes this temptation by producing opioid blockade early in detoxification. Comparable success rates of outpatient clonidine and naltrexone detoxification and inpatient clonidine detoxification support this hypothesis as well as the conclusion that combination clonidine and naltrexone therapy should be a more widely practiced treatment for opiate withdrawal. However, the doses of naltrexone used in the protocol are smaller than those available commercially. The purpose of this study was to develop an outpatient clonidine and naltrexone protocol using naltrexone doses available to all treatment programs. Although, the use of larger naltrexone doses risks precipitation of a more intense withdrawal and an outpatient setting may limit the amount of clonidine which may be necessary to ameliorate this withdrawal syndrome, outpatient detoxification is a desirable mode of treatment for both patients and physicians.
1. **SUBJECTS**

The patient group included 18 heroin abusers, 10 men and 8 women, treated at the Substance Abuse Treatment Unit of the Connecticut Mental Health Center, New Haven, Connecticut. As shown in table 1, mean age (± S.D.) was 30.0 years (± 4.1) and mean duration of opioid use was 8.4 years (± 6.3). Types of opiates abused included: intravenous heroin (n=16), intranasal heroin (n=3), intravenous hydromorphone (Dilaudid) (n=2), intravenous methadone (n=1), oral oxycodone (Percocet) (n=1), and oral meperidine (Demerol) (n=1). Of note, 6 of the patients who were using intravenous heroin stated that they were using synthetic opiates (i.e. "Liberty," "Blue Thunder," etc.). Polydrug abuse included: intravenous cocaine (n=7), intranasal cocaine (n=2), marijuana (n=13), benzodiazepines (n=2), and alcohol abuse (n=4). Eleven patients had undergone prior substance abuse treatment including detoxification (n=8), methadone maintenance (n=3), and naltrexone maintenance (n=4). The mean naloxone challenge test score on the Wang scale (Wang, 1982) was 16.1 (±1.5).

All patients participating in the study were in good health as evidenced by a physical examination, medical history, psychiatric screening interview, laboratory analysis, and ECG performed one week prior to the detoxification. Laboratory analysis included a CBC, LFT's, VDRL, Hepatitis screening, and urinalysis. In addition, any woman participating in the study received a Beta-HCG pregnancy test. Candidates were excluded from the study if they: 1) were
younger than 18 years or older than 45 years, 2) had a systolic blood pressure greater than 165 or a diastolic blood pressure greater than 110, or were undergoing medical treatment for hypertension, 3) were receiving current treatment for other medical conditions requiring ongoing medication, 4) had been treated with tricyclic antidepressants, MAO inhibitors, or phenothiazines during the two weeks prior to participation, 5) were allergic to imidazoline drugs, 6) had a history of acute or chronic hepatitis, cardiac arrhythmias, rheumatic fever, sinus bradycardia of less than 50 bpm, renal or metabolic disease, 7) had a history of a severe psychiatric disorder (e.g., major psychotic episode, schizophrenia, psychotic depression, bipolar affective disorders), or 8) were pregnant. (All women participating in the study had a negative Beta-HCG test within one week of the study.)

2. TREATMENT SCHEDULE

Patients were divided into two treatment cohorts. Patients referred to the Substance Abuse Treatment Unit for detoxification in the first half of the study underwent a 5 day detoxification. Detoxification time was then reduced to 4 days for all patients in the second half of the study. On day 1 patients in the first cohort underwent a naloxone challenge test followed by clonidine therapy administered three times a day. On the subsequent 4 days patients received a combination of clonidine and naltrexone therapy. Naltrexone was given in a single morning dose on days 2 through 5. Supplementary clonidine doses were available to patients on days 2 and 3. For those patients in the second half of the study days 1 and
2 of the detoxification were combined. On day 1 patients in the second cohort also underwent a naloxone challenge test followed by clonididine therapy administered three times a day. However, unlike the original cohort, these patients received their first naltrexone dose in the afternoon of their first day. All subsequent naltrexone doses were advanced one day. Both protocols are summarized in Table 2.

Patients came to clinic daily at 8-9 am to receive medication, answer questionnaires, and have their blood pressure monitored. Patients in the first cohort were required to remain in clinic from 8:30 am to 3:00 pm on the first three days of the study so that their withdrawal symptoms could be followed, blood pressure and heart rate monitored, and clonididine doses adjusted accordingly. Patients in this group were not permitted to work on the second and third days, and were not permitted to drive on the first three days. They were asked to remain at home these first three evenings. In order to minimize orthostatic blood pressure effects, patients were instructed to sit when urinating and to avoid hot showers. For the second cohort these restrictions only applied to the first two days. When a "significant other" picked the patient up at the conclusion of the first day of the study, the study was explained to them and they were asked to sign the patient's consent form. An investigator was on call each evening to respond to questions.

While in clinic both groups had their blood pressure monitored immediately before, 60 minutes after, and 120 minutes after each clonididine dose. Subjective and objective abstinence rating scales were filled out at these times as well as immediately before and 60 minutes after the patient's daily naltrexone dose. Patients took a
prescribed evening dose of clonidine home with them as well as 0.1 to 0.3 mg for "prn" doses. They were asked to fill out a subjective abstinence rating scale at 8:00 pm before taking their evening dose of clonidine and also to return extra pills the following morning.

On days 1, 2 and 3 additional clonidine doses were given one hour following daily naltrexone doses if the patient had 5 or more of the 17 signs and symptoms of withdrawal included in our abstinence rating scale. Clonidine doses were tapered or held, if standing systolic blood pressure was less than 80 mm Hg, if diastolic pressure was less than 60 mm Hg, or if patients complained of orthostatic symptoms.

Naltrexone therapy was begun on day 2 for the patients in the first cohort and was administered at 9:00 am (30 minutes following the am clonidine dose). This initial dose was 12.5 mg or one fourth of the 50 mg scored naltrexone tablet (Trexan). This dose was increased to 25 mg on day 3, 50 mg on day 4, and 100 mg on day 5 (usually a Friday). All naltrexone doses were administered at 9:00 am. Patients then entered a naltrexone maintenance program the following Monday to continue their naltrexone therapy.

Patients in the second cohort began their naltrexone on the first day of the protocol, receiving 12.5 mg of naltrexone at 1:30 pm (30 minutes following their second clonidine dose and two to three hours following their NCT). They then received 25 mg at 9:00 am on day 2, 50 mg on day 3, and 50 or 100 mg on day 4 depending on the day of week and what day they would enter the naltrexone maintenance program (Tuesday or Thursday patients received 50 mg; Monday, Wednesday, or Friday patients received 100 mg).
Patients were given chloral hydrate, 1 gm, as indicated for insomnia. For patients who did not respond to chloral hydrate, or who experienced muscular aching not relieved by clonidine, flurazepam 30 mg or diazepam 10 mg was prescribed in place of chloral hydrate.

Urine samples were obtained on days 1, 3, and 5 from the first cohort and days 1, 3, and 4 from the second cohort. These were analyzed to evaluate any use of illicit drugs.

3. NALOXONE CHALLENGE TEST

The degree of a street addict's opiate dependence is difficult to determine because of unreliable histories and variable opiate concentrations found in illicit preparations. Through the naloxone challenge test we were able to establish opiate dependence as well as determine the degree of that dependence. We could then more reliably estimate initial clonidine doses and ensure a more comfortable detoxification. The naloxone challenge test was described by Wang in 1974 (Wang, 1974) and modified in 1977 and 1982 (Weisen, 1977; Wang 1982). It consists of an intramuscular injection of 0.8mg naloxone followed by scoring of withdrawal symptoms at 10, 20, and 30 minutes. The Wang rating scale scores objective symptoms of withdrawal, giving more weight to symptoms if they appear more rapidly (See Table 3). Patients received clonidine after 10 or 20 minutes if their predicted score on Wang's 36 point scale was greater than 9 at those times, otherwise they received clonidine at 30 minutes. An additional clonidine dose was given one hour later if their Wang abstinence score remained above
5. Patients without symptoms at 10 minutes received an additional 0.8 mg naloxone intramuscularly. Individuals whose score was less than 2 at 30 minutes after their second injection of naloxone (total of 1.6 mg naloxone), were told that they did not have a clinically recognizable acute withdrawal syndrome, were dropped from the study, and were referred to a naltrexone maintenance program. Day 1 clonidine doses, based on naloxone challenge test scores, are listed in Table 4.

4. INSTRUMENTS

Throughout the course of the detoxification, patients' objective and subjective symptoms of withdrawal were closely monitored using withdrawal scales from previous detoxification studies at the Connecticut Mental Health Center (Charney, 1981; Charney, 1982; Kleber, in press). Every morning prior to medications, patients were asked to complete a withdrawal line, craving line, opiate withdrawal scale (self-rated), and a self-rated visual analog scale. The withdrawal line is a 100 millimeter long horizontal line that functions as an analogue scale. The left end of the line is marked "0 - no withdrawal" and the right end is marked "100 - severe withdrawal." In addition, patients completed this scale before and 60 minutes following their daily naltrexone dose. Similar to the withdrawal line, the craving line is a 100 millimeter horizontal line with its left end marked "0 - no craving" and the right end marked "100 - severe craving." The opiate withdrawal symptom checklist is a self-rated analogue scale containing 38 statements pertaining to symptoms of opiate withdrawal (e.g., "My bones and joints have been
aching") (Haertzen and Meketon, 1968). Patients rated each of these statements on a 1 (not at all) to 4 (very much) point scale. The self-rated visual analogue scale contains five symptoms (energy, nervousness, irritability, uninvolvement, and unpleasantness) which patients rated on a 1(low) to 7(high) point scale.

In addition to the rating scales completed every morning by the patients, observer-rated abstinence rating scale (ARS) were completed for each patient at specific time intervals throughout each day. The ARS monitors 17 signs and symptoms associated with opioid withdrawal (see Table 5). On the first day of the detoxification, the ARS was measured before the NCT, immediately after the NCT but before any clonidine was given, at 30, 60 and 120 minutes after the initial clonidine dose, and immediately before the 2:00 pm clonidine dose. On subsequent days, the ARS was measured in the morning prior to any medication, before the daily naltrexone dose, 60 minutes after the naltrexone dose, and immediately before the 2:00 pm clonidine.
RESULTS

A. OUTCOME

1. Acute Detoxification

Eighteen patients underwent a naloxone challenge test (NCT). One had a negative challenge test (Wang score below 2 after a total naloxone dose of 1.6 mg) and was dropped from the study. Of the seventeen patients who entered the protocol, nine began the 5 day detoxification, and eight began the 4 day detoxification. Of the nine patients who entered the 5 day study, eight successfully completed detoxification (89%) and were discharged on maintenance doses of naltrexone. The patient who failed to complete the study had a peak NCT score of 15. This score was comparable to the mean peak NCT score for the patients completing the protocol (15.5 +/- 3.3). Throughout the first day she complained of considerable discomfort from leg cramps unrelieved by clonidine. These were relieved in the afternoon of the first day by warm soaks. Despite this relief, the patient failed to return the morning of the second day. She returned to the Substance Abuse Treatment Unit and was subsequently detoxified as an inpatient with methadone. She then entered the naltrexone maintenance program for a brief period before leaving to enroll in methadone maintenance.

Of the eight patients who entered the 4 day study, six successfully completed detoxification (75%) and were discharged on maintenance doses of naltrexone. The two patients who failed to complete the study were similar in that they both experienced less discomfort
than most patients, but failed to return for the fourth and final day of the protocol. The first had a NCT score of 16 at 10 minutes, comparable to the mean peak NCT score (+/- S.D.) of 17.0 (+/- 3.3) for the patients completing the protocol. This patient returned to clinic on the following day (day 5) stating that he had used intravenous heroin the preceding evening (confirmed by urine toxicology screen). Repeated efforts to restart him on naltrexone were unsuccessful. The second patient had a peak NCT score of 9 after 1.6 mg of naloxone. She never returned to the clinic despite repeated efforts by phone to reestablish contact. Of note, because these patients had completed 3 days of the 4 day protocol, they had achieved a maintenance dose of naltrexone (50 mg/day).

2. **Follow-up**

Six of the eight patients (75%) completing the 5 day protocol began naltrexone maintenance the week following their detoxification. Both of the patients who had failed to enter naltrexone maintenance had moved out of the area that same week. Arrangements had been made for one of these patients to enter naltrexone maintenance in the area to which she was moving; however, she failed to report to that naltrexone maintenance program. One month after completing the protocol, five of these six patients remained in naltrexone maintenance.

Four of the six patients (67%) completing the 4 day protocol began naltrexone maintenance the week following their detoxification. One month after completing the protocol all four of these patients remained in naltrexone maintenance. The two patients who failed to
enter a naltrexone maintenance program were again using opioids one month after completing the detoxification.

B. RESPONSE TO OPIOID ANTAGONISTS (NALOXONE AND NALTREXONE)

Opioid antagonists precipitated significant withdrawal symptoms, but symptoms were adequately relieved by clonidine. The mean Wang score for all patients following the NCT was 16.1 (+/− 5.1), corresponding to a methadone dose requirement of 40 mg/day by Wang's criteria (Wang 1982). On day 1, both cohorts responded well to clonidine given at 10 or 20 minutes (depending on the patient's NCT score) following the intramuscular naloxone. By 30 minutes after receiving clonidine patients in both cohorts had experienced symptom relief as demonstrated by the abstinence rating scale (ARS). Two hours after the first oral dose of clonidine, patients in both cohorts had lower ARS scores than prior to the NCT. This reflects both the efficacy of clonidine in relieving symptoms as well as the half-life of naloxone (approximately 60 minutes).

Patients in cohort 2 received their first dose of naltrexone (12.5mg) on the first day, two hours after receiving their initial dose of clonidine. Of note, only two patients (NCT scores= 20 and 6) experienced an increase in their ARS scores 60 minutes after this naltrexone dose. Even with the increase, each of these patients' ARS scores were less than 5.

Patients in the first cohort received their first dose of naltrexone (12.5mg) on the second day, 30 minutes following their morning dose of clonidine. Only one patient (NCT score=16) experienced an
increase in symptoms, and these symptoms responded well to a supplementary clonidine dose.

Both groups of patients experienced a rise in their ARS score the morning of their second day before any medication had been given. This responded well to the morning dose of clonidine, and probably represented the time lag between their 8pm and 9am dose of clonidine. Although many had taken 0.1-0.2mg of clonidine for discomfort during the night, this was still less than their regular clonidine dose. This morning pre-medication rise in ARS score was also experienced on day 3 by the patients in the 5 day detoxification. This was not experienced on days 3 or 4 by those in the 4 day detoxification, when they were receiving a maintenance dose of naltrexone (50mg and 50 to 100mg, respectively).

Unlike patients in the 4 day detoxification, those in the 5 day detoxification experienced transient rises in ARS on days 3 and 4, sixty minutes following their daily naltrexone dose. When patients' ARS exceeded a score of 5, they were given supplementary doses of clonidine and responded well to them. On day 5, all patients received 100 to 150 mg naltrexone without any symptoms.

C. ABSTINENCE SYMPTOM RELIEF

The treatment regimen effectively suppressed signs and symptoms of withdrawal. On no day was the mean number of signs and symptoms greater than 5 out of the 17 included in the abstinence rating scale (Figure 1). Persistent symptoms were anxiety, restlessness, insomnia, muscle aches, and "yen" for sleep. Often the signs and symptoms reported were mild in nature.
Through the course of the detoxification patients experienced significant symptom relief (5 day detoxification $F(5,47)=6.6$, $p<.005$; 4 day detoxification $F(4,29)=4.5$, $p<.01$). There was no significant difference between the two groups (treatment $F(1,63)=.3$). There was a significant correlation between NCT score and mean ARS scores for patients in both groups on days 1 and 2 (Day 1, $p < .05$; Day 2, $p < .01$), which accounted for 30% to 45% of the variance in ARS.

Patient ratings of withdrawal (Figure 2), indicated that the withdrawal process was relatively comfortable for the majority of patients. On this scale, the mean withdrawal line for those in the 4 day detoxification was significantly higher than for those in the 5 day (treatment $F=6.3$, $p<.025$). This difference was also shown on the opiate withdrawal scale (treatment $F=16.5$, $p<.005$), another patient rated analogue scale shown in Figure 3. However, elimination of baseline differences by examination of the percentage change from day 1 of these withdrawal scale scores demonstrates no difference between the two treatments (Figure 3B). Craving lines (Figure 4) and patient rated analogue scales (Table 6) for both detoxification groups did not differ or change significantly over the course of the detoxifications.

D. BLOOD PRESSURE CHANGES AND SIDE EFFECTS OF CLONIDINE

The effects of the clonidine-naltrexone treatment on standing systolic and diastolic blood pressure and standing and supine heart rate are summarized in figures 5 through 8. As shown in Figure 5, clonidine significantly lowered systolic blood pressure for both groups (4 day detoxification $F(5,35)= 6.0$, $p< .005$; 5 day
detoxification $F(6,55)=2.6$, $p<.05$). On days 1 through 4 for those in the 5 day detoxification, and days 1 through 3 for those in the 4 day detoxification, systolic blood pressure differed significantly from the "initial" values (paired t test $p<.01$). The decrease in systolic blood pressure for those in the 4 day detoxification was not significantly greater than that for those in the 5 day detoxification ($F=2.6$, $p<.25$). Clonidine significantly lowered the diastolic blood pressure (Figure 6) of the patients in the 4 day protocol ($F(5,35)=5.4$, $p<.005$); however, the diastolic blood pressure of patients in the 5 day protocol was not significantly lowered ($F(6,55)=2.1$, $p<.1$). Diastolic blood pressure on days 1 through 4 for patients in both detoxification groups differed significantly from "initial" values (paired t test $p<.005$ to $p<.025$). As shown in figures 7 and 8, clonidine did not significantly alter standing and supine heart rates of patients in the 4 day detoxification (standing $F(5,35)=.6$; supine $F(5,35)=1.9$). The standing heart rate (figure 7) of patients in the 5 day detoxification was not significantly decreased by clonidine ($F(6,55)=.8$); however, supine heart rate (Figure 8) was significantly decreased by clonidine ($F(6,55)=2.7$, $p<.05$). This is probably reflective of the bradycardic effects that clonidine may produce at rest which are overridden when standing or exercising (Pettinger, 1975). There were no syncopal episodes during the course of treatment; however, most patients reported dizziness on standing during days 2 and 3. There was no significant difference between the groups in mean total clonidine required per day. In both groups, patients with NCT scores greater than 20 did not have significantly larger decreases in blood pressure or heart rate than did patients with NCT less than 20.
Other commonly reported side effects from clonidine were dry mouth and sedation.

E. PATIENT COMPLIANCE

Patients took evening clonidine doses as instructed and returned unused clonidine in the morning when they reported to clinic. One patient in the 5 day detoxification used intravenous heroin on the evening of the first day. She was allowed to continue in the protocol and experienced no adverse effects when she received the full scheduled dose of naltrexone on the second day. Two patients in the 4 day detoxification used intravenous cocaine on the afternoon of the third day (confirmed by urine toxicology screen) and experienced euphoria.
DISCUSSION

1. CLINICAL OUTCOME

The clonidine-naltrexone outpatient detoxification enabled 14 of 17 (82%) opioid dependent patients to completely withdraw from short acting opioids within a 4 or 5 day period and simultaneously begin naltrexone maintenance. This success rate is higher than that achieved using either of the standard methods of outpatient detoxification: gradual methadone taper (13% to 46 %) (Wilson, 1974; Wilson, 1975; Silsby, 1974; Senay and Dorus, 1981; Washton and Resnick, 1981), or clonidine alone (31% to 40%) (Washton and Resnick, 1981; Kleber, 1985). The results of this study are comparable to the success rate achieved in a similar outpatient regimen enabling 12 of 14 (86%) heroin users to withdraw from opioids in 5 days (Kleber, in press). Although the earlier study also enabled a high percentage of patients to withdraw from short acting opioids and attain maintenance levels of naltrexone on an outpatient basis, the present 5 or 4 day detoxification allowed a more rapid withdrawal with a simplified, single-dose-per-day naltrexone regimen. Such a regimen significantly reduced the period of time patients spent in clinic without significantly increasing daily clonidine doses or changes in blood pressure.

Comparison of the two detoxification groups in this study demonstrate that initiating naltrexone therapy sooner significantly shortened the withdrawal syndrome without increasing observer-rated symptomatology. Patients in the 5 day detoxification began naltrexone therapy on the second day of the detoxification with
maintenance levels (50 mg) achieved by the fourth day. Patients in the 4 day group began naltrexone therapy on the first day of the detoxification and achieved maintenance levels by the third day, forty-eight hours after their last opioid use. Comparison of the abstinence rating curves of both groups (Figure 1) shows almost complete abstinence relief in the third day of the protocol for those in the 4 day study, a level achieved on the fourth day by those in the 5 day study. Another advantage of receiving naltrexone on the first rather than second day of detoxification was that patients were less likely to use opioids in the early stages of the detoxification, before complete opioid blockade had been achieved.

Although there was no significant difference between the two groups in observer-rated withdrawal symptomatology, there was a significant difference in patient-rated symptomatology (Figures 2 and 3). Because there were significant baseline differences between the two groups on both these withdrawal scales, the baseline differences were adjusted by examining percentage change from day 1 (Figures 2B and 3B). With this adjustment, no significant difference was found between the treatments.

The clonidine and naltrexone combination worked well in the outpatient setting. Signs of opioid withdrawal were rarely seen, and patients reported mild withdrawal symptoms. The symptoms not relieved by clonidine were primarily restlessness, muscle aches, and insomnia, which were more likely to persist in patients with higher NCT scores. Those in the 4 day study with persistent restlessness or muscle aches were prescribed diazepam 10 mg twice a day on days 1 and 2. They experienced significant relief from this intervention.
Clonidine significantly lowered standing blood pressures on the first three days of the study for each group; however, no clinical problems resulted from this and patients were not working or driving on these days. Many patients in both groups requested that clonidine doses be held by the fourth day of the protocol to alleviate the sedation that they were experiencing. At this time in the study, clonidine doses could be quickly tapered without the consequence of withdrawal symptoms arising or rebound hypertension occurring (Pettinger, 1975; Pettinger, 1980; Hansson, 1973).

Limitations of outpatient treatment emerged. Of the three patients who withdrew from the study, two had already attained maintenance levels of naltrexone. One of these two patients was relatively asymptomatic, but failed to return to clinic the morning of the fourth and final day. The following week he returned to the outpatient clinic, but never began naltrexone maintenance. His failure to complete the detoxification despite achieving maintenance naltrexone levels with mild withdrawal symptomatology probably reflects the ambivalence many addicts have about remaining drug-free; it is unclear whether inpatient detoxification would have been more successful in detoxifying this patient. The other patient had the lowest NCT score, with a maximum of 8, 10 minutes after receiving her second 0.8 mg dose of naloxone (total naloxone dose = 1.6 mg). She had been dependent on oral oxycodone and experienced considerable gastrointestinal cramps on the second and third days of the protocol, which were unrelieved by clonidine. The anticholinergic, antispasmodic agent atropine 0.4 mg was prescribed three times a day in an effort to counteract the rebound increase in
gastrointestinal activity probably responsible for her discomfort (Lord, 1977; Burks, 1976); however, this was also ineffective. Although somewhat milder, the abstinence syndrome associated with oxycodone resembles that of morphine and lasts approximately 7 days (Charney and Kleber, 1980). Gastrointestinal cramping may have been more of a problem for this patient because the oral route of her opioid administration would sensitize her gastrointestinal opioid receptors to a greater degree than intravenous or intranasal routes. This would be a phenomenon unique to oxycodone, since detoxification from oral methadone does not produce such gastrointestinal discomfort even when withdrawal is precipitated using the clonidine naltrexone combination (Charney, 1982). In a previous study using clonidine to detoxify a patient addicted to oxycodone, the patient did not complain of any gastrointestinal discomfort throughout the detoxification (Charney and Kleber, 1980). It is possible that the addition of naltrexone, an oral opioid antagonist, so early in the detoxification of these patients may precipitate significant gastrointestinal symptoms through its antagonistic action directly on their sensitized gastrointestinal opioid receptors. Clonidine therapy alone may be the detoxification of choice in oral oxycodone users followed by institution of naltrexone maintenance when their gastrointestinal opioid receptors are not as sensitive to its effects.

The third patient who did not complete the detoxification began the 5 day study but did not return after the first day. She had a NCT of 16, and experienced considerable muscle cramps in her legs throughout the first day, which were eventually relieved by warm
soaks. In later detoxifications, diazepam, 10 mg twice a day, was successful in alleviating persistent muscle cramps which some patients experienced. This lack of intervention may have affected her continued participation in the study.

Unlike the previous clonidine-naltrexone outpatient detoxification, this protocol did not include a week of naltrexone therapy following the detoxification. Instead, patients continued naltrexone maintenance at one of the two naltrexone maintenance programs offered by the Substance Abuse Treatment Unit. Ten of 14 (72%) patients who completed the detoxification returned for naltrexone maintenance. In the week following detoxification, patients had their blood pressures measured and signs and symptoms rated using the abstinence rating scale. Only two patients complained of symptoms sometimes associated with the stabilization period of naltrexone therapy (Hollister, 1981; Kleber and Kosten, 1984).

2. NALOXONE CHALLENGE TEST (NCT)

The naloxone challenge test (NCT) established opioid dependence in patients requesting detoxification. One of the 18 (5.6%) patients who entered the study had a negative NCT, a rate less than the 15% to 34% of negative naloxone challenges found in patients applying for methadone maintenance (Blachley, 1973, Wang, 1982). The NCT also served to guide initial clonidine doses by quantifying the degree of patients' dependence. Day 1, 2, and 3 clonidine doses varied directly with NCT scores. Although NCT scores aided in the determination of clonidine doses, abstinence rating scale (ARS)
scores as well as blood pressure measurements ultimately
determined how much clonidine patients would receive. This
flexibility in clonidine doses ensured a safer and more effective
detoxification.

This study demonstrated a significant correlation between NCT and ARS scores for patients on the days 1 and 2 of the study (Day 1, p < .05; Day 2, p < .01). The NCT, a measurement of the degree of a patient's addiction, accounted for 30% to 45% of the variance in ARS scores on those days.

3. MECHANISM OF ACTION OF CLONIDINE AND NALTREXONE IN OPIOID WITHDRAWAL

Clonidine attenuates the opioid withdrawal syndrome by suppressing the rebound noradrenergic hyperactivity which occurs when chronic opioid administration ceases (Korf, 1974; Llorens, 1978; Maas, 1979). It accomplishes this by binding presynaptically to alpha-2 adrenergic receptors, mimicking feedback inhibition to the locus coeruleus, the brain's major noradrenergic nucleus (Aghajanian, 1978; Crawley, 1979; Nathanson and Redmond, 1981; Laverty and Roth, 1981). Since lesions of noradrenergic neurons do not reduce clonidine's ability to decrease some behavioral signs of opioid withdrawal, mechanisms other than this presynaptic one have also been postulated (Britton, 1984). Recent studies suggest that clonidine also has anti-withdrawal effects on the amygdala (Freedman and Aghajanian, in press), spinal cord (Franz, 1982), and the forebrain (Matsui and Yamamoto, 1984).
Naltrexone precipitates withdrawal by binding to opioid receptors. This produces a rapid reversal in the morphine induced increase in the number of alpha-2 and beta receptors (Hamburg and Tallman, 1981) as well as reversing the opioid agonist induced deficiency in endogenous opioid function (Kosterlitz and Hughes, 1975). These changes should produce a briefer, less severe withdrawal syndrome.

Naltrexone also appears to equalize the time course of heroin and methadone withdrawal (Charney, 1982; Charney, 1986; Kleber, in press). The effects of naltrexone on methadone pharmacokinetics may be related to the reduction in the duration and symptoms of methadone withdrawal. Naloxone is thought to increase serum methadone levels in addicted patients by displacing methadone from opioid receptor sites (Resnick, 1979). Investigators have postulated that the clonidine-naltrexone regimen equalizes the length of the heroin and methadone withdrawal syndromes by this same mechanism. By displacing opioids from binding sites, naltrexone would eliminate the effect of opioid half-life on the time course of central noradrenergic normalization and of the withdrawal syndrome (Kleber, in press).

In previous studies, administration of clonidine and naltrexone in combination to opioid dependent patients dramatically shortened the withdrawal syndrome without significantly increasing patient discomfort (Charney, 1982; Charney, 1986; Kleber, in press). The present study demonstrates that naltrexone, administered even earlier in detoxification, continued to shorten the withdrawal
syndrome without dramatically altering withdrawal symptomatology.

An interesting effect of the addition of larger doses of naltrexone to the detoxification has been the decrease in the amount of clonidine required. Table 7 demonstrates the difference in mean daily clonidine doses for both inpatient and outpatient detoxifications using clonidine. Kleber and colleagues used clonidine and naltrexone in combination to detoxify heroin addicts. Naltrexone therapy began on day 2 using 1 mg doses which were increased every 4 hours by 1 mg increments. This detoxification used significantly more clonidine than both the 4 and 5 day studies (4 day, $p \leq .001$; 5 day, $p \leq .01$). This difference might be explained by the difference in naltrexone dosage regimens. Patients in Kleber's study were given multiple small doses of naltrexone on days 2 and 3. This study administered the same total daily amount of naltrexone in a single morning dose. Small numerous doses like those used in Kleber's study might precipitate withdrawal repeatedly throughout days 2 and 3, increasing patient's withdrawal symptomatology and necessitating more total clonidine. A single large dose of naltrexone, although it initially precipitates withdrawal, is enough to remain on more opioid receptors for a longer period of time. Withdrawal is not precipitated repeatedly throughout the day, patients withdrawal symptomatology is not increased, and patients do not require additional clonidine. Lower clonidine doses, especially in the outpatient setting, is an additional advantage of this present study.

Charney's studies detoxified patients from methadone maintenance (Charney, 1981; Charney, 1982). Both the patients
given clonidine therapy alone (Charney, 1981) and the patients given combination clonidine and naltrexone (with the naltrexone given in multiple, small doses), required significantly more clonidine than the 4 and 5 day regimens described here (p < .001). This probably reflects the difference in the amount of clonidine required to detoxify patients from long-acting opioids such as methadone versus the clonidine required to detoxify patients from short-acting opioids such as heroin. When identical naltrexone dosage regimens are used and the amount of clonidine required per day to detoxify patients from methadone (Charney, 1982) is compared to the amount of clonidine per day required to detoxify heroin addicts (Kleber, in press), a significantly greater amount of clonidine is required to detoxify methadone patients (p < .001).

4. CLINICAL IMPLICATIONS

Although not definitive treatment for opioid dependence, withdrawal is the first step towards opioid abstinence. Methadone taper, clonidine therapy alone, and clonidine and naltrexone in combination are all effective therapeutic strategies developed towards this goal. Although equivalent to outpatient methadone taper, the efficacy of clonidine alone has been less favorable in outpatient than inpatient studies (Kleber et al., 1985). Combination clonidine and naltrexone therapy has been shown effective in both the inpatient and outpatient settings (Charney, 1982, Kleber et al., in press). However, these previous studies used small, multiple dose per day naltrexone regimens which could be conducted only by programs which had access to liquid naltrexone, a form not
commercially available. This study has further improved the availability of the clonidine-naltrexone combination by using a single dose per day naltrexone regimen with naltrexone doses available to any opioid treatment facility. Day 1 naltrexone doses are 12.5 mg, one quarter of the scored 50 mg naltrexone tablet (Trexan). As the study was conducted, some additional advantages became evident: the withdrawal syndrome produced by this detoxification was significantly shortened without significantly increasing patient discomfort at any point; no more clonidine was required by the patients in the 4 day study than what was needed by those in the 5 day study or previous clonidine-naltrexone studies (Charney et al., 1982; Kleber, in press); patients spent less time in clinic but continued to receive adequate monitoring of hypotension and sedation, both potentially dangerous side effects of clonidine; the clonidine naltrexone outpatient detoxification was effectively integrated with an outpatient naltrexone maintenance clinic so that maintenance doses of naltrexone as well as outpatient counseling could be continued without interruption.

This study demonstrated that combination clonidine-naltrexone therapy using commercially available doses of naltrexone is an effective therapeutic avenue in outpatient heroin detoxification. The time course and patient comfort of this regimen make it a useful, attractive, and efficacious outpatient method for treating the acute opioid withdrawal syndrome. This technique can now be more widely used in the treatment of opioid dependence. In detoxifications which are not conducted for research purposes, a NCT would not be needed to substantiate opioid dependence. Neither
clonidine nor naltrexone possess any agonistic activity at opioid receptors and no addictive potential, qualities of methadone that previously attracted "pseudoaddicts" to enlist in methadone maintenance. Instead, 0.2 mg clonidine three times a day could be administered on day 1, and modifications could be made based on a patient's blood pressure and abstinence rating scale measurements. Examination of this revised clonidine dosage schedule as well as treatment of methadone maintained patients with an outpatient protocol are the next logical steps in the investigation of this treatment regimen.
TABLE 1

Characteristics of Patients

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<th>5 Day Detox</th>
<th>4 Day Detox</th>
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<td>30.1 (+/-4.5)</td>
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<tr>
<td>NCT Score</td>
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<td>15.9(+/-2.3)*</td>
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*Mean NCT of all those beginning study. Mean NCT of those who completed 5 day detoxification was unchanged; however, mean NCT for those who completed 4 day detoxification was 17.0 (+/-3.3).

#N = 8, one patient in this group had a negative NCT

Note: NCT = naloxone challenge test score from Wang (1982) with range = 0-36 (see Table 3).
# TABLE 2

## CLONIDINE AND NALTREXONE DOSAGE SCHEDULE

<table>
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<tr>
<th>TIME</th>
<th>DRUG</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>DAY 4</th>
<th>DAY 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5D</td>
<td>4D</td>
<td>5D</td>
<td>4D</td>
<td>5D</td>
</tr>
<tr>
<td>8:30 am</td>
<td>Naloxone</td>
<td>0.8 mg IM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clonidine</td>
<td>0.1-0.3 mg</td>
<td>0.1-0.2 mg</td>
<td>0.1-0.2 mg</td>
<td>0.1 mg</td>
<td>0.1 mg</td>
</tr>
<tr>
<td>9:00 am</td>
<td>Clonidine</td>
<td>0.1-0.3 mg</td>
<td>12.5 mg</td>
<td>25 mg</td>
<td>25 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:00 am</td>
<td>Naltrexone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:00 pm</td>
<td>Clonidine</td>
<td>0.1-0.3 mg</td>
<td>0.1-0.3 mg</td>
<td>0.1-0.2 mg</td>
<td>0.1-0.2 mg</td>
<td>0.1 mg</td>
</tr>
<tr>
<td>8:00 pm</td>
<td>Clonidine</td>
<td>0.1-0.3 mg</td>
<td>0.1-0.3 mg</td>
<td>0.1-0.2 mg</td>
<td>0.1-0.2 mg</td>
<td>0.1 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>Clonidine</strong></td>
<td><strong>.3-.9 mg</strong></td>
<td><strong>.3-.9 mg</strong></td>
<td><strong>.3-.6 mg</strong></td>
<td><strong>.3-.6 mg</strong></td>
<td><strong>.3 mg</strong></td>
</tr>
<tr>
<td><strong>Daily</strong></td>
<td><strong>Naltrexone</strong></td>
<td><strong>-</strong></td>
<td><strong>12.5 mg</strong></td>
<td><strong>12.5 mg</strong></td>
<td><strong>25 mg</strong></td>
<td><strong>25 mg</strong></td>
</tr>
</tbody>
</table>

*Clonidine 0.1-0.3 mg was available on an as-needed basis following each naltrexone dose on days 1, 2, and 3. Each evening patients were given clonidine 0.1 to 0.2 mg to use at home in addition to their evening dose.

**Note: 5D = 5 day detoxification; 4D = 4 day detoxification*
TABLE 3

Rating Scale of Withdrawal Symptoms after .8mg IM Naloxone*

Score for presence or absence of symptomatology:

<table>
<thead>
<tr>
<th>Symptomatology</th>
<th>10 min.</th>
<th></th>
<th>20 min.</th>
<th></th>
<th>30 min.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Gooseflesh</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Profuse sweating</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Restlessness</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation and nasal congestion</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Uncontrollable yawning</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*from Wang (1982); maximum score = 36.
<table>
<thead>
<tr>
<th>Predicted NCT Score (10 minutes)</th>
<th>Oral Clonidine HCL (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;18</td>
<td>0.3 0.1-0.2 0.2</td>
</tr>
<tr>
<td>9-17</td>
<td>0.2 0.1 0.1-0.2</td>
</tr>
<tr>
<td>&lt;9 but &gt;0</td>
<td>0.1-0.2 0.1 0.1</td>
</tr>
</tbody>
</table>
### ABSTINENCE RATING SCALE

**Subjective Symptoms**

- Craving
- Anxiety
- Restlessness
- Insomnia
- Muscle Aching
- Anorexia
- Nausea
- Hot and Cold Flashes

**Objective Symptoms**

- Rhinorrhea
- Tremors
- Perspiration
- Yawning
- Yen for Sleep
- Gooseflesh
- Vomiting
- Diarrhea
- Lacrimation
TABLE 6

PATIENT- RATED ANALOGUE SCALES

<table>
<thead>
<tr>
<th>COHORT</th>
<th>5D</th>
<th>4D</th>
<th>5D</th>
<th>4D</th>
<th>5D</th>
<th>4D</th>
<th>5D</th>
<th>4D</th>
<th>5D</th>
<th>4D</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.9</td>
<td>2.2</td>
<td>2.8</td>
<td>3.2</td>
<td>2.5</td>
<td>3.2</td>
<td>2.9</td>
<td>1.8</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>1.6</td>
<td>2.5</td>
<td>2.5</td>
<td>4.0</td>
<td>3.4</td>
<td>3.0</td>
<td>3.8</td>
<td>3.5</td>
<td>3.4</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>3.7</td>
<td>2.3</td>
<td>3.5</td>
<td>2.8</td>
<td>3.0</td>
<td>2.9</td>
<td>2.7</td>
<td>3.8</td>
<td>2.3</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>3.7</td>
<td>2.0</td>
<td>2.5</td>
<td>2.0</td>
<td>3.2</td>
<td>1.8</td>
<td>2.5</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>5</td>
<td>3.9</td>
<td>-</td>
<td>2.1</td>
<td>-</td>
<td>2.1</td>
<td>-</td>
<td>2.1</td>
<td>-</td>
<td>2.4</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: 5D = 5 day detoxification  
4D = 4 day detoxification
### TABLE 7

**COMPARISON OF DAILY CLONIDINE DOSES (MEAN +/-SD)**

<table>
<thead>
<tr>
<th>Study</th>
<th>4 Day</th>
<th>5 Day</th>
<th>Kleber, in press</th>
<th>Charney, 1982</th>
<th>Charney, 1981</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.5 +/-0.2</td>
<td>0.5 +/-0.1</td>
<td>0.5 +/-0.2</td>
<td>1.1 +/-0.2</td>
<td>1.0 +/-0.2</td>
</tr>
<tr>
<td>2</td>
<td>0.5 +/-0.2</td>
<td>0.6 +/-0.1</td>
<td>1.1 +/-0.5</td>
<td>2.9 +/-0.6</td>
<td>1.0 +/-0.2</td>
</tr>
<tr>
<td>3</td>
<td>0.3 +/-0.1</td>
<td>0.4 +/-0.1</td>
<td>0.6 +/-0.3</td>
<td>2.3 +/-0.6</td>
<td>1.0 +/-0.2</td>
</tr>
<tr>
<td>4</td>
<td>0.3 +/-0.8</td>
<td>0.1 +/-0.1</td>
<td>0.3 +/-0.3</td>
<td>0.9 +/-0.2</td>
<td>1.1 +/-0.3</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>0.3 +/-0.5</td>
<td>0.2 +/-0.2</td>
<td>0.5 +/-0.3</td>
<td>1.1 +/-0.3</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>0.1 +/-0.1</td>
<td>0.2 +/-0.1</td>
<td>1.1 +/-0.3</td>
</tr>
</tbody>
</table>

Note:

**4 Day** = 4 days of combination clonidine and naltrexone therapy with naltrexone given in a single morning dose.

**5 Day** = 1 day of clonidine therapy (after NCT) followed by 4 days of combination clonidine and naltrexone therapy with naltrexone given in a single morning dose.

**Kleber, in press** = 1 day of clonidine therapy (after NCT) followed by 4 days of combination clonidine and naltrexone therapy with naltrexone given in multiple small doses throughout the day.

**Charney, 1982** = same as Kleber, in press, but inpatient study detoxing methadone patients.

**Charney, 1981** = inpatient study using clonidine alone to detoxify methadone patients.

Analysis by Z test showed significant differences between A and B (days 2 - 4, p < .01), A and C (days 2 - 4, p < .001), A and D (days 1 - 4, p < .001), A and E (days 1 - 4, p < .001), B and C (days 2 and 5, p < .001; days 3 and 4, p < .01), B and D (days 1 - 5, p < .001), and B and E (days 1 - 5, p < .001).
FIGURE 1
ABSTINENCE RATING SCALE (MEAN) VS DAY

Abstinence Rating Scale, mean

Day
Figure 1: Abstinence Rating Scale (Mean) per Day
Mean number of signs and symptoms per patient per day, as rated on the 17 item observer-rated abstinence rating scale. The two detoxification groups were analyzed by 2-way ANOVA for repeated measure for the first 4 days. Time effect: $F(3,63)=15.1, p<.0001$; Treatment effect: $F(1,63)=.3, p>.25$; Interaction: $F(3,63)=1.9, p<.25$). 1-way ANOVA analysis of each detoxification showed significant changes in mean ARS per day over the 4 or 5 days (5 day $F(5,47)=6.6, p<.005$; 4 day $F(4,29)=4.5, p<.01$).
FIGURE 2

WITHDRAWAL LINE (MEAN) VS DAY

withdrawal line (mean), mm

Day

4 day (n=6)

5 day (n=8)
Figure 2: Mean Withdrawal Line per Day
Mean withdrawal line measurement for each day. The "withdrawal line" is a horizontal 100 millimeter line that functions as an analogue scale. The left end is labeled "0- no withdrawal" and the right end is labeled "100- severe withdrawal." Curves represent mean scores for patients in the 5 or 4 day detoxification. The two plots are significantly different as analyzed by 2-way ANOVA for repeated measures for the first 4 days. Treatment: F(1,63)=6.3, p<.025; Time effect: F(3,63)=8.5, p<.005; Interaction: F(3,63)=3.3, p<.05).
FIGURE 2B
PERCENTAGE INCREASE WITHDRAWAL LINE (MEAN)

VS DAY

Withdrawal line (mean)

4 DAY (n=6)

5 DAY (n=8)

Day
Figure 2B: Percentage Increase Opiate Withdrawal Line (mean) per Day

Percentage increase from day 1 opiate withdrawal line for each day. The two detoxifications are not significantly different by 2-way ANOVA for repeated measure for the first 4 days (treatment: \( F(1,63) = .629, \ p > .25 \)). There was a significant time effect and interaction (time effect: \( F(3,63) = 6.4, \ p < .005 \); interaction: \( F(3,63) = 3.3, \ p < .05 \)).
FIGURE 3

WITHDRAWAL SCALE (MEAN) VS DAY

Withdrawal scale (mean)

Day

4 day (n=6)

5 day (n=8)
Figure 3: **Mean Opiate Withdrawal Scale per Day**

Mean opiate withdrawal scale score for each day. The opiate withdrawal scale is a symptom checklist that functions as a self-rated analogue scale. It contains 38 statements pertaining to opiate withdrawal (e.g., "My bones and joints have been aching") which patients rate on a 1 (not at all) to 4 (very much so) point scale. The highest possible score is 152 points. The two detoxifications are significantly different by 2-way ANOVA for repeated measure for the first 4 days (treatment: $F(1,63)=16.5$, $p<.005$; time effect: $F(3,63)=3.6$, $p<.025$); however, there was not a significant interaction ($F(3,63)$, $p>.25$). Only the 5 day detoxification showed a significant change per day as analyzed by 1-way ANOVA for repeated measures (treatment: $F(4,39)=4.5$, $p<.01$).
FIGURE 3B

PERCENTAGE INCREASE WITHDRAWAL SCALE (MEAN)

VS DAY

Percentage change (mean)

Day

5 day (n=8)

4 day (n=6)
Figure 3B: Percentage Change Opiate Withdrawal Scale (mean) per Day. Percentage change from day 1 opiate withdrawal scale for each day. The two detoxifications are not significantly different by 2-way ANOVA for repeated measure for the first 4 days (treatment: F(1,63) = .105, p > .25). There was a significant time effect and interaction (time effect: F(3,63) = 5.9, p < .005; interaction: F(3,63) = 4.5, p < .01).
FIGURE 4

CRAVING LINE (MEAN) VS DAY

Craving line (mean), mm

4 day (n=6)

5 day (n=8)

Day
Figure 4: Mean Craving Line per Day
Mean craving line measured each morning (prior to the administration of any medications) for each day. The craving line is a 100 millimeter horizontal line with its left end labeled "0 - no craving" and its right end labeled "100 - severe craving." Ratings significantly decreased over time for both groups by 2-way ANOVA for repeated measures for the first 4 days ($F(3,63)=4.8$, $p<.01$). The two detoxifications did not differ significantly.
FIGURE 5
SYSTOLIC BLOOD PRESSURE (MEAN) PER DAY
Figure 5: Mean Systolic Blood Pressure (Standing) per Day
Standing systolic blood pressure (BP) for each day. Day "0" represents "initial" systolic BP, which is the mean for all subjects of two measures; one taken the morning of the first day of the detoxification prior to the administration of any medications, and the other taken at least three days prior to each patient's entry into the study. The measurements corresponding to ".5 day" represent each patient's systolic BP immediately after the NCT prior to the administration of any clonidine. Day 1 measurements represent the mean of all systolic BP measurements taken at least one hour after the NCT and initial clonidine dose. Overall changes in systolic BP were significant as analyzed by 1-way ANOVA for repeated measures (5 day treatment F(5,35)=2.6, p<.05; 4 day treatment F(5,35)=6.0, p<.005). By 2-way ANOVA for repeated measures there was not a significant difference between treatments for the first 4 days (treatment: F(1,95)=2.6, p<.25; interaction: F(5,95)= .7, p<.25).
FIGURE 6

DIASTOLIC BLOOD PRESSURE (MEAN) PER DAY

Day

Diastolic BP (mean), mmHg

5 DAY

4 DAY

0 1 2 3 4 5 6
Figure 6: Mean Diastolic Blood Pressure (Standing)
Standing diastolic blood pressure (BP) for each day. Graph clarifications as in figure 5. The two groups were significantly different (treatment: F(1,95)=5.8, p<.025) and had a significant change over time (F(5,95)= 8.2, p<.0001) as analyzed by 2-way ANOVA for repeated measures for the first 4 days; however, there was not a significant interaction (F(5,95)=.3, p>.25).
FIGURE 7

STANDING HEART RATE (MEAN) PER DAY

Day

Standing HR (mean), beats/min.

4 day

5 day
Figure 7: Mean Heart Rate (Standing) per Day
Mean standing heart rate (HR) for each day. Graph clarifications as in figure 5. For each detoxification group, overall changes in standing HR were not significant as analyzed by 1-way ANOVA for repeated measures. Also, the two groups were not significantly different as analyzed by 2-way ANOVA for repeated measures for the first 4 days.
FIGURE 8

SUPINE HEART RATE (MEAN) PER DAY

Supine HR (mean), beats/min.

Day

4 day
5 day
Figure 8: *Mean Heart Rate (Supine) per Day*

Mean supine heart rate (HR) for each day. Graph clarifications as in figure 5. For patients in the 5 day detoxification, overall changes in supine HR were significant as analyzed by 1-way ANOVA for repeated measures (F(6,55)=2.7, p<.05). There were no significant changes in supine heart rate for patients in the 4 day detoxification by this analysis. The two groups differed significantly (F(1,95)=3.9, p<.05) and had a significant change over time (F(5,95)=6.0, p<.005) as analyzed by 2-way ANOVA for repeated measures. There was not a significant interaction (F(5,95)=.6, p>.25).
REFERENCES


Haertzen CA, Meketon MJ. (1968) Opiate withdrawal as measured by the Addiction Research Center Inventory (ARCI). *Dis Nerv Syst* 29:450-455.


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DATE