Buprenorphine Treatment of Heroin Dependence
(Detoxification and Maintenance)
in a Private Practice Setting

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ABSTRACT. At the conclusion of a 3-year demonstration project in a medical setting in which refusal to accept methadone was an inclusion criterion, 12 subjects were unable to detoxify from buprenorphine and remained adamant in their refusal to enroll in a MMTP. In order to study the feasibility of expanding opportunities for treatment previously unavailable to this under-served population of heroin addicts, these 12 subjects plus an additional 11 subjects (N = 23) were recruited for a 12 months trial of buprenorphine treatment conducted in an office-based setting on a fee-for-service basis. An additional cohort of 40 heroin dependent subjects were entered in a protocol for detoxification only. The findings demonstrate both feasibility and patient acceptance of office based fee-for-service buprenorphine treatment, supporting the need for (1) additional studies of this population and (2) changes in government regulations to reintroduce addiction treatment under physician auspices in private practice settings. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2001 by The Haworth Press, Inc. All rights reserved.]
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INTRODUCTION

Numerous studies\textsuperscript{1-4} have shown that buprenorphine is an acceptable and effective modality. Additionally, buprenorphine makes treatment available for many heroin addicts who refuse other treatments, such as methadone maintenance.\textsuperscript{5} The present study originated following termination of a 3-year NIDA-funded demonstration project conducted in the Faculty Practice Offices of New York University Medical Center. To recruit subjects at the outset of that study, we placed an ad in a local NYC newspaper.* The day this ad appeared, we were inundated with 85 responses from individuals who were unwilling to receive methadone maintenance but willing to volunteer for a study of buprenorphine. All subsequent subjects were recruited simply by word of mouth, with no further need to advertise.

Conclusions from this project were:

1. Maintenance on buprenorphine in an outpatient general medical facility is acceptable to many heroin-addicted individuals who would otherwise remain outside the treatment system, due to their refusal to enter a methadone maintenance treatment program or a residential therapeutic community;
2. By increasing the dose, frequency of clinic visits for administration of buprenorphine can be reduced from daily to 3-4 days per week, without the need to dispense take-home doses;
3. A wide range of maintenance doses is effective in reducing heroin craving and use;
4. Emergence of abstinence symptoms, particularly anergia, makes discontinuation of buprenorphine difficult to achieve.

From a public health point of view, our most significant finding, was that there is a large subgroup of heroin addicts who are unwilling to receive

*On heroin and want treatment? If you, or someone you know, is using heroin and not willing to enter a methadone maintenance treatment program or residential therapeutic treatment program, there is a NYU study that may be of help. The study is testing the effectiveness of buprenorphine, a medication used to reduce pain in patients after surgery. Buprenorphine is more potent than methadone or morphine, but is much safer because it produces little physical dependence and patients do not become overly sedated or “high.” Those interested should call the Buprenorphine Treatment Project at: 212-XXX-XXXXX.
methadone maintenance or enter residential treatment, but want and will respond to another treatment modality. Unlike stereotypes of heroin addicts, this group consisted primarily of individuals with relatively high levels of social adjustment, as indicated by employment, lack of criminal activity and marital status. In contrast to the addicted professional, such as a physician or nurse, this population was made up of average people who could be your neighbor or co-worker. The tragedy, however, is that the majority of this group were unable to receive any treatment for their addiction under the existing treatment system (since past attempts to detoxify were unsuccessful and they were unwilling to accept methadone maintenance or enter a therapeutic community).

At the completion of the three-year grant, when funds for this project terminated, we made every attempt to detoxify the patients from buprenorphine and refer them for continued treatment. A small group succeeded in detoxification (and continued in drug-free treatment with naltrexone) and a few accepted transfer to our MMTP at Bellevue Hospital. However, 12 subjects, who had been doing well on buprenorphine, were unable to detoxify and remained adamant in their refusal to enroll in a MMTP.

It appeared counter to the best interest of the patient, and bordering on the unethical, for us arbitrarily to discontinue an apparently successful therapy in these twelve subjects. In addition, a primary thrust of our research interest was to make treatment of opioid dependence more widely available than present policy permits.

The initial study was located in the Faculty Practice Offices of the Medical Center. It demonstrated positive results of a freestanding buprenorphine treatment program in a general medical facility, unaffiliated with methadone maintenance and free of stigma or association with the heroin addicted culture. However, the project’s funding was terminated and we had an interest in exploring the feasibility of conducting a similar office-based addiction treatment program, which included buprenorphine maintenance, on a fee-for-service basis. In this way we could study the feasibility of expanding the opportunities for treatment previously unavailable to this under-served population of heroin addicts. Consequently, these patients were transferred to a private psychiatric practice for continued buprenorphine treatment.

**SUBJECT CRITERIA**

Eligibility for participation included heroin dependence (DSM-IV 304.00), a minimum age of 18 years, not currently pregnant, no other substance dependence, no serious illness or psychoses, the ability to pay for private
treatment, a signed informed consent, and refusal to be hospitalized or enroll for methadone maintenance treatment.

**CLINICAL PHARMACOLOGY**

Buprenorphine exerts its analgesic effect via high affinity binding to the \( \mu \) subclass of opiate receptors in the central nervous system. Although buprenorphine may be classified as a partial agonist, under the conditions of recommended use it behaves very much like a classical \( \mu \) agonist such as morphine. One unusual property of buprenorphine observed in *in vitro* studies is its very slow rate of dissociation from its receptor. This could account for its longer duration of action than morphine, the unpredictability of its reversal by opioid antagonists, and its low level of manifest physical dependence.

Buprenorphine demonstrates narcotic antagonist activity and has been shown to be equipotent with naloxone as an antagonist of morphine in the mouse tail flick test. However, naloxone may not be effective in reversing the respiratory depression produced by buprenorphine. Buprenorphine demonstrates a bi-phasic dose-response curve, with orally administered doses beginning to plateau at around 35 mg and higher doses producing smaller opioid effects.

Three-tenth mg (0.3) of the commercial preparation (Buprenex) administered parenterally is approximately equivalent to 10 mg morphine sulfate orally in analgesic and respiratory depressant effects in adults. Pharmacological effects occur as soon as 15 minutes after intramuscular injection and persist for 6 hours or longer. Peak pharmacological effects usually are observed at 1 hour. When used intravenously, the times to onset and peak effect are shortened. In postoperative adults, pharmacokinetic studies have shown elimination half-lives ranging from 1.2-7.2 hours (mean 2.2 hours) after intravenous administration of 0.3 mg of buprenorphine. A ten-patient pharmacokinetic study suggests that the clearance of the drug may be higher in children than in adults. This is supported by at least one repeat-dose study in postoperative pain that showed an optimal inter-dose interval of 4-5 hours in pediatric patients as opposed to the recommended 6-8 hours in adults. Numerous clinical studies have demonstrated that by sublingual administration in addicted individuals, 8 mg buprenorphine produces approximately equipotent effects to 60 mg methadone.

**METHODS**

At the conclusion of the NYU study, the twelve patients who were unable to detoxify from buprenorphine were referred to a private, fee-for-service
psychiatric practice. An additional eleven subjects were recruited, *de novo*, from word-of-mouth referrals, for a total cohort of twenty-three subjects (N = 23). The psychiatric nurse clinician who coordinated the study at NYU was hired to coordinate this study. All patients received individual and/or group psychotherapy conducted by clinical social workers or the nurse clinician and psychiatric evaluation/medication management by a psychiatrist.

Buprenorphine was offered for up to 12 months. Doses were individualized to a maximum of 16 mg/day. All doses were administered single blind under direct observation. Take-home doses were not provided. When both physician and nurse were not available, doses were provided to a local community pharmacy for administration by a pharmacist. Subjects had the option of receiving a double dose every 2 days and a triple dose every 3 days, reducing the frequency of visits needed for medication administration. All subjects received individual and/or group psychotherapy at least weekly. All subjects received a psychiatric evaluation and were prescribed psychotropic medication, if indicated. Random urine drug screens were done on subjects who claimed to be abstinent.

**RESULTS (DEMOGRAPHIC CHARACTERISTICS)**

Ages ranged from 20-52 years with a mean age of 36.1 years. There were sixteen males and seven females with a racial breakdown of nineteen White, three Hispanic and one Black. Thirteen of the participants were married, three were separated or divorced and seven were single. Sixteen worked full time, three worked part-time while living with employed spouses, one was a student and three were unemployed living with parents.

Years of education ranged from nine to nineteen (mean = 12.9 years). Heroin use ranged from $50-$150 per day (mean = $75.3 per day). Of the twenty-three participants, criminality was essentially absent, with only one (a drop-out) committing petty theft to support his habit. One-half (13/23) never had been enrolled in methadone maintenance—the remaining 10 subjects had previously received methadone maintenance, but said they would never again. The majority (N = 16) had comorbid depression, with Beck Scores that warranted adjunctive anti-depressant medication.

**OUTCOME (DOSES)**

Most subjects received 8 mg/day (range 5-16 mg/day) and attended the clinic for medication only 3-4 days/wk. The two subjects who continued to receive buprenorphine daily were husband and wife, and we postulate that
this arrangement satisfied their psychological needs for daily contact with the staff, rather than their having a pharmacological need for the medication.

The following chart shows buprenorphine doses received, number of subjects and frequency of administration:

<table>
<thead>
<tr>
<th>DOSE</th>
<th>N =</th>
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<tbody>
<tr>
<td>5 mg/day</td>
<td>2</td>
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<tr>
<td>7 mg/day</td>
<td>1</td>
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<tr>
<td>8 mg/day</td>
<td>13</td>
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<td>10 mg/day</td>
<td>3</td>
</tr>
<tr>
<td>12 mg/day</td>
<td>3</td>
</tr>
<tr>
<td>16 mg/day</td>
<td>1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FREQUENCY</th>
<th>N =</th>
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<tbody>
<tr>
<td>3 days/wk</td>
<td>12</td>
</tr>
<tr>
<td>4 days/wk</td>
<td>9</td>
</tr>
<tr>
<td>7 days/wk</td>
<td>2</td>
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**OUTCOME (DRUG USE)**

Outcome with respect to drug use status shows that three subjects were terminated within the initial 2 months for irregular attendance. Most subjects (N = 16) remained heroin abstinent throughout, and 4 subjects used heroin intermittently, with a frequency of 1-4 days per month.

Follow-up at 6 months (for N = 20), shows only 4 subjects discontinued buprenorphine and remained abstinent, 5 enrolled in MMTP and about half (N = 11) had relapsed to heroin.

**DETOXIFICATION**

In addition to maintenance, we also used buprenorphine for outpatient detoxification in 40 subjects. Inclusion criteria were the same as for maintenance and the subjects’ demographic characteristics were similar. The participants ranged in age from 21-51 years, with a mean of 36.1. Thirty-two were male and 8 were female. Thirteen of the participants were married, 3 were separated or divorced, and twelve were single. Education ranged from nine to
twenty years with a mean of 15.2 years. Income per year ranged from $13,000-600,000 (mean: $17,900).

**HEROIN USE DATA**

The level of dependence varied widely, ranging from $10–$200 per day with a mean $67.3. Although the mean age of 1st use (25.9 years) and dependence (26.9 years) occurred while in the mid 20’s, there was a large spread ranging from early teens to early 40’s (14-39 years and 14-42 years, respectively). Prior detoxification ranged from none (for 7 subjects, this was their first attempt to detoxify) to as many as 30 prior attempts with a mean of 5.9 attempts.

**DOSING**

The initial dose administered was approximately 1 mg per $10/day heroin, given 15-20 hours after the last heroin administration. The daily dose decrements were 2.0 mg/day at doses greater that 10 mg, 1.0 mg/day at doses between 10 mg and 5 mg, 0.5 mg/day at doses between 5 mg and 1 mg, and 0.1-0.2 mg/day at doses between 1 mg and zero. This was followed by a placebo for 14-17 days. As doses approached zero, all subjects experienced abstinence symptoms, most distressing being a profound feeling of lethargy and anergia.

**TREATMENT DATA**

The dose on day one ranged from one to twenty-four mg (mean = 9.7 mg). Subjects received buprenorphine for 3-36 days (mean = 18 days). Dropout and relapse occurred only when doses were reduced to less than 2 mg. Twenty-nine of the 40 subjects completed the detoxification protocol, receiving buprenorphine for 10-34 days (mean = 22.3 days) and then placebo for an additional period of up to 17 days (mean = 9.6 days). Naltrexone was started in > 25% of subjects (N = 11 of 40).

Follow-up data at 3 months and 12 months for the detoxification subjects are as follows: of the initial 40 subjects, 17.5% (N = 7) were abstinent at 3 months and 10% (N = 4) remained abstinent at 12 months. Four of the seven subjects not using heroin at three months were receiving naltrexone treatment. All those who relapsed stated they would have chosen to receive maintenance with buprenorphine, if this had been available to them.
DISCUSSION

There are two clinical issues concerning dosing with buprenorphine which are important to emphasize: (1) Before receiving the first dose of buprenorphine a sufficiently long period of time should have elapsed so that the initial buprenorphine dose does not produce precipitated abstinence. The best way to determine this is to ascertain that withdrawal symptoms have already started. Sometimes subjects are not truthful about how long it has been since they last self-administered heroin and sometimes it may take a longer time for high doses of heroin to dissociate from the receptor. Longer acting opioids, such as methadone, may require an opiate-free period of 20 hours or longer to safely administer the first buprenorphine dose without precipitating abstinence; (2) During the period of detoxification abstinence symptoms of profound anergia may appear. This symptom is particularly difficult for individuals who are working or have child-care responsibilities. Our approach to minimize this difficulty was to use very small decrements in buprenorphine doses, particularly as the dose approached zero and to follow this by a period of 14-17 days on buprenorphine placebo, until the individual was able to start treatment with naltrexone. If given the choice, most subjects preferred not to know the day they receive the last dose of buprenorphine, unless protection from readdiction by naltrexone could begin.

CONCLUSIONS

The findings demonstrate both feasibility and patient acceptance of office-based fee-for-service buprenorphine treatment for heroin dependence. Amending federal regulations to expand buprenorphine to private practice settings may offer significant public health benefits by improving addiction treatment delivery and reducing heroin use, without creating an undue risk to public safety. Further evaluations of office-based buprenorphine treatment should be encouraged.

Initially, we recommend its use be restricted to physicians with advanced training in addiction medicine and/or those who specialize in AIDS treatment, limiting the numbers of patients at each office and creating clear standards and regulations regarding doses and take-home. Cogent arguments that support changing the federal regulations to include using methadone in office-based addiction treatment have been clearly elucidated, with no significant increase in diversion anticipated. A recent NIH Consensus Statement recommended this change be made in methadone regulations. As a partial agonist, buprenorphine seems even more appropriate than methadone for this purpose.
REFERENCES


