Outpatient Treatment of Opiate Dependence with Sublingual Buprenorphine/Naloxone versus Methadone Maintenance: a Randomized Trial of Alternative Treatments in Real Life Settings

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A. Study Purpose and Rationale

Opiate Dependence is a major public health concern in this country, affecting an estimated one million adults. Opiate maintenance therapy with methadone has been the standard of care since the 1970's but methadone maintenance has been limited to specialized clinics and daily attendance is usually required. Many patients complain that this inconvenience interferes with their ability to work. There are currently approximately 1200 methadone maintenance centers in the Unites States and they serve an estimated 15% percent of opiate addicts. Long wait times, often a few months, exists for entrance into such programs. Thus more accessible alternatives have been investigated. Buprenorphine hydrochloride is a partial opiate agonist approved by the Food and Drug Administration (FDA) for sublingual use in the outpatient setting by qualified physicians in 2000. Potential advantages over methadone include reduced potential for dependence and abuse. Furthermore, because qualified physicians may write prescriptions for up to a 30-day supply from their office, it may reduce the inconvenience and social stigma that is currently associated with opiate maintenance therapy. The most popular formulation in this country is Suboxone®, manufactured by Reckitt Benckiser Pharmaceuticals, which is a combination sublingual tablet of buprenorphine hydrochloride and naloxone hydrochloride. Naloxone hydrochloride is an opiate antagonist with minimal sublingual or oral bioavailability. It is included in the formulation to further reduce abuse potential, since intravenous injection would precipitate an opiate withdrawal syndrome. There have been several short-term studies comparing the two medications in closely monitored settings but none comparing traditional methadone maintenance to buprenorphine/naloxone with flexible dosing and take-home doses, as it is currently being used in offices throughout the United States.

B. Hypotheses

Opiate-dependent individuals treated at methadone maintenance centers have better long-term retention in treatment than those in outpatient treatment with buprenorphine/naloxone. Subjects treated with buprenorphine/naloxone will have less self-reported opiate use and percentage of opiate-negative urine tests and will be more likely to be employed and have consistent housing than their counterparts on methadone maintenance.

C. Study Design and Statistical Analysis

This is a prospective randomized trial to assess the effectiveness of sublingual buprenorphine/naloxone versus oral methadone for long-term treatment of opiate dependence as each is practiced in a real life clinical setting, with flexible dosing schedules. Subjects will be followed for one year. The primary outcome is retention in treatment at three months (defined by both positive verification of attendance at treatment center and self report of persistence with study medication). Secondary outcomes include retention in treatment at one, two, six, nine, and twelve months after induction. Additional outcomes will be measured at initiation and at one, three, six, nine, and twelve months and include self-reported opiate use (over previous 7 and 30 days), percentage of urine samples positive for opiates and other drugs of abuse, and self-reported employment and housing (over previous 30 days).

Subjects will be recruited by advertisements placed in the New York City subway system, *Metro* free morning newspaper, and the *Village Voice*. Advertisement text will read, "Do you have a problem with heroin or opiates? Do you want help? Research study under way now. No waiting list. No charge for medications. Call 1-800-GET-CLEAN." When people call they will speak with a trained research assistant who will explain the study and if they are interested an appointment will be arranged with a physician investigator. A physician will establish eligibility based on inclusion and exclusion criteria defined below. The physician will explain the two treatments including the naloxone component of the sublingual treatment and the danger that injection of the medication would likely precipitate an opiate withdrawal syndrome. Informed consent will be obtained by a physician.

Eligible and consented subjects will be randomized to either the buprenorphine/naloxone group or the methadone group using computer-generated random order numbers and stratified according to previous methadone treatment or not, in order to maximize similarity between the two groups with this factor known to affect retention in previous studies. Subjects in the methadone group will be scheduled appointments at a participating methadone clinic in New York City for within two weeks. Subjects in the buprenorphine/naloxone group will be scheduled appointments with a participating qualified physician in New York City, also within two weeks. At each site the usual standard practices for prescription of each medication will proceed, including dose adjustments. At each site, urine toxicology testing will be performed at least weekly for the first two months and usual counseling services will be provided. Patients will be seen as frequently as is standard at each center, usually daily for methadone maintenance and daily for the first few weeks of buprenorphine/naloxone then less frequently at the physician's discretion.

Additionally, patients will be seen by the study investigators at t=0, 1, 2, 3, 6, 9, and 12 months. At t=0, also the time of randomization, an intake questionnaire will be completed to collect demographic data and information about possible risk factors such as homelessness, employment, support structures, previous treatment for drug dependence. Self-reported opiate use will be reported by number of days used in last seven and last thirty days. They will do the same for other drugs of abuse. Subjects will report the amount of time employed over the previous month reported as not employed, employed less that one week, employed 1-2 weeks, or employed greater than two weeks of the past months. Subjects will report the stability of their housing using the same categorization. They will confirm if they are still taking the study medication and they will be asked to estimate the number of days missed in the previous week and month. They will also be asked to report adverse events at that time and blood will be drawn for safety monitoring purposes, specifically to test liver function tests. At those times, the investigators will verify retention in treatment by confirming with the treatment center that the patient has been to a visit within the preceding two weeks.

All measures will be analyzed with an intention to treat analysis. The study will be powered to detect a difference of 15% in retention at 3 months. Retention in treatment will be compared at 1, 2, 3, 6, 9, and 12 months. Results will be compared using a two-tailed chi-square analysis assuming a power of 0.8 and an alpha 0.05. It is calculated that 175 subjects will be needed in each group to detect a significant difference at three months. For secondary outcomes, the effects of treatment over time will be analyzed according to repeated measures analysis of variance (ANOVA). Logistic regression analysis will be employed to identify factors associated with improved retention in treatment.

Urine toxicology tests will be performed as per usual practices at each treatment center, which will be in most cases once per week. In addition, urine toxicology testing will be performed at each interval visit with the investigators (i.e. at one, two, three, six, nine, and 12 months). Prior to commencement of the study it will be confirmed that each laboratory's immunoassay is consistent with federal guidelines that consider less than 300 ng/ml of drug or metabolite to be negative for that substance, except for amphetamines, in which case the cut-off value is 1000 ng/ml.

At each visit with study investigators (i.e. at 1, 2, 3, 6, 9, 12 months), testing will include liver function tests, complete blood counts, chemistry profiles, and serum β-HCG for females with childbearing potential. If liver transaminases (AST/ALT) increase more than 3 times baseline values, a review process will occur by study investigators in conjunction with the treating physician. If it is felt that

the change in liver function is possibly due to study medication, the study medication will be discontinued for safety reasons. If a female subject becomes pregnant during the study period, discussion will occur between the subject and her treating physician, with the investigative physicians acting as advisors, regarding the risks and benefits of continuing on the study medications.

D. Study Drugs

a. Methadone

Methadone is an FDA-approved oral medication for the treatment of opiate dependence. Because it is a full opiate agonist it decreases cravings and withdrawal symptoms for people who are dependent on opiates. Its relatively long duration of action of approximately 24 hours accounts for the decrease in abuse potential and the psychological swings that characterize much of addiction to illicit drugs. It is a Schedule II narcotic and has been shown to be safe and efficacious and has been used in clinical practice since the 1920's. Since the 1970's the FDA has been regulating its administration in controlled clinical settings. The dosage regimen used in the study is not prescribed except to say that it will be consistent with clinical practices otherwise performed by the providers. This is because the dose of methadone required to reduce cravings varies widely from patient to patient and is influenced by the amount and chronicity of their opiate use patterns but also by individual metabolism. Metabolism may be affected by other medications, including those that affect the P450 3A4 enzyme. The usual dose range for methadone maintenance is 80-120 mg. Common side effects include nausea, vomiting, constipation, dizziness, drowsiness, weakness. Also reported are weight gain (80%), constipation (70%), increased intake of fluids (63%), delayed ejaculation (60%), increased alcohol use (40%), increased frequency of urination (37%), paresthesias (32%), hallucinations (17%) (Bloom).

b. Buprenorphine Hydrochloride

Buprenorphine hydrochloride is a partial agonist at the μ-opiate receptor. It has a high affinity at the receptor and a long duration of action, approximately 24 hours. Because it is a partial agonist, there is a "ceiling effect" with regards to action at the receptors, with a resultant decrease in potential for respiratory depression and euphoria than is seen with full agonists including methadone. Buprenorphine is a Schedule III narcotic whose sublingual formulation was approved by the FDA in 2000 for use in opiate dependence in the outpatient setting by a qualified physician. Qualified physicians must meet certain criteria (please see appendix). Induction to buprenorphine requires that a patient be exhibiting signs of opiate withdrawal (e.g. piloerection, diarrhea, abdominal cramps, mydriasis). Initial dose is usually 4mg and this may be repeated in a few hours until symptoms of opiate withdrawal subside. Most often, the same dose is given the next day, with some adjustment over the first few days to few weeks to reach the dose at which patients report alleviation of withdrawal symptoms and decrease in cravings. The usual maintenance dose is 12-24 mg. During the first two days, patients are treated with buprenorphine alone (no naloxone) to prevent possible naloxone-precipitated opiate withdrawal symptoms. If a patient misses more than approximately five doses, re-induction is necessary. If a patient is doing well on a steady dose, at the treating physician's discretion, take-home doses will be prescribed for up to 30 days. Each qualified physician may treat a maximum of thirty patients at any given time.

In this study, buprenorphine will be used in combination with naloxone, in the sublingual tablet Suboxone®, manufactured by Reckitt Benckiser Pharmaceuticals. Suboxone® is currently available in two strengths of buprenorphine/naloxone: 2/0.5mg and 8/2 mg. Adverse events reported for buprenorphine/naloxone include headache (36%), withdrawal syndrome (25%), pain (22.4%), insomnia (14%), nausea (15%), abdominal pain (11.2%), constipation (12.1%) and less that 10% reported rhinitis, diarrhea, infection, chills, back pain, vasodilation or flushing, vomiting, or weakness (Fudala 2003)

c. Naloxone Hydrochloride

Naloxone is an opiate antagonist. It is most frequently used in intravenous form to treat opiate toxicity. In oral form, it may be used (off-label) for opiate-induced constipation. It has limited sublingual

or oral bioavailability and in the doses used in this study and is included for the purpose of reducing potential for abuse, as described above. Please see above for side effect profile.

E. Medical Device

No medical devices will be used

F. Study Questionnaires

Questionnaires will be completed at t=0,1,2,3,6,9, and 12 months. The questionnaires are not available at this time. Please see above description in the Study Design and Statistical Analysis section.

G. Study Subjects

Eligible subjects will meet DSM-IV criteria for opiate dependence (see below) and will be between the ages of 18 and 59. They must have a urine toxicology positive for opiates and negative for methadone at initiation. Patients will be excluded if they report being in treatment with methadone or buprenorphine in the previous 30 days, if they have a diagnosis of alcohol dependence or of dependence to any substances other than nicotine or caffeine. They will be excluded if there is a history of schizophrenia, bipolar disease, or serious psychiatric condition other than depression or anxiety, except in the case of history of psychotic symptoms or suicidal/homicidal ideations or attempts. Subjects will be excluded if they have a medical condition including unstable cardiovascular of liver disease, poorly controlled diabetes, HIV disease, or active tuberculosis. Patients taking anticonvulsant medications or disulfiram will be excluded. Women who are pregnant or breast feeding will be excluded and all women with childbearing potential who wish to participate must agree to use contraception and will be informed that they will be removed from the study if they become pregnant.

After consent is obtained and eligibility criteria reviewed, screening tests will be performed. All subjects must have urine negative for methadone and positive for methadone, negative serum β-HCG test for females to rule out pregnancy, liver function tests and general chemistries will be done for baseline values and subjects with AST/ALT greater than 2x the upper limit of normal will be excluded. Subjects will be counseled and tested for Hepatitis B and C and HIV using standard ELISA tests, with confirmation via Western Blot and/or DNA viral load studies when positive. Subjects with positive serology for viral hepatitis will be included in the study unless their AST or ALT is greater than 2x the upper limit of normal as described above. Subjects who are HIV positive will be provided counseling and referrals for medical care but will be excluded from the study.

H. Recruitment of Subjects

Please see above description in Study Design section.

I. Confidentiality of Study Data

Each subject will be given a unique study identification number at the time of randomization. All questionnaires will be coded with this number in lieu of identifying information.

J. Potential Conflict of Interest

None

K. Location of the Study

Columbia University Medical Center, methadone maintenance centers and qualified buprenorphine providers in New York City (as yet to be determined).

L. Potential Risks

Both methadone and buprenorphine have opiate agonist effects and should not be used in combination with other sedating agents including other opiates, benzodiazepines because of the risk of respiratory depression. Buprenorphine may cause increased liver transaminases, especially in people with underlying liver disease. If injected, naloxone may cause an opiate withdrawal syndrome which is quite unpleasant and may include abdominal pain and cramps, diarrhea, muscle pain and spasm, but is not fatal. Please see above descriptions of Study Medications for adverse events. Risks of phlebotomy include minor pain and very small risk of infection or bleeding.

M. Potential Benefits

Decreased use of intravenous heroin causes reduced risk of blood-borne infections including HIV and Hepatitis C. Studies have shown improvement in employment and reduced crime on methadone maintenance. Study participants will have short wait-times for entrance into treatment. They will be provided counseling services as well.

N. Alternative Therapies

a. Buprenorphine without Naloxone
LAAM (levo-alpha acetyl methadol), rarely used in the US currently
Non-pharmacologic treatments including Twelve-Step programs, group and individual counseling
No treatment

O. Compensation to Subjects

Subjects will be compensated with two thirty-dollar Metrocards at each visit with the investigators

P. Costs to Subjects

Not applicable

Q. Minors as Research Subjects

Not applicable

R. Radiation or Radioactive Substances

Not applicable

Appendix

DSM-IV criteria for substance dependence (Kauffman J F 1995):

1) tolerance to the drug, as defined by either of the following: • the need for markedly increased amounts of the substance to achieve intoxication or desired effect • markedly diminished effect with continued use of the same amount of the substance
2) withdrawal, as manifested by either of the following: • the characteristic withdrawal syndrome for the substance • use of the same (or closely related) substance to relieve or avoid withdrawal symptoms
3) the substance is often taken in larger amounts or over a longer period than was intended
4) persistent desire or unsuccessful efforts to cut down or control substance use
5) a great deal of time spent in activities necessary to obtain or use the substance or to recover from its effects
6) important social, occupational, or recreational activities given up or reduced because of substance use
7) continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem that was likely to have been caused or exacerbated by the substance.

Buprenorphine may be prescribed by a "Qualified Physician," who

- Is licensed by a state medical board AND
  - Underwent 8 hrs of training by American Psychiatric Association, American Society of Addiction Medicine, or others
  - OR is board certified in Addiction Medicine
  - Must obtain waiver from federal government
  - May not treat more than 30 patients concurrently (includes all providers in group practice)
  - Has capacity to refer for appropriate counseling and ancillary services