BUPRENORPHINE FOR ACUTE HEROIN DETOXIFICATION: A RETROSPECTIVE COMPARISON TO CLONIDINE

by

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CERTIFICATE OF APPROVAL

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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ABSTRACT

Heroin use is a significant and escalating public health concern in both the United States and the Portland metropolitan area. Although prevalence of heroin use is relatively low compared to other health risks, burden of disease is significant. For users, heroin dependence is associated with job loss, arrest, and serious health conditions including infectious disease and fatal overdose. For the community, heroin dependence has significant impact on decreased work productivity, increased crime, and increased health care expenditures.

Medical treatment for heroin dependence is often divided into three phases: (1) managed withdrawal treatment, or detoxification; (2) continued treatment, for stabilization and sobriety; and (3) maintenance treatment and/or psychosocial therapy, for continued abstinence. This study examines detoxification. Pharmacotherapies include methadone, clonidine, and, recently, buprenorphine. Each drug has different pharmacological action and corresponding effectiveness in relieving withdrawal symptoms. Methadone is the most common treatment for maintenance, but its usefulness for detoxification is limited. Clonidine has been the primary option for heroin detoxification outside federally regulated Opioid Treatment Programs (i.e., methadone clinics), but is unable to alleviate many withdrawal symptoms. In contrast, buprenorphine has unique pharmacological characteristics that produce improved withdrawal symptom relief compared to clonidine, and recent federal legislation makes buprenorphine more widely available than methadone.

Hooper Detoxification Center is a 24-hour community-based treatment center that offers medical detoxification from heroin and other addictive substances. In June 2004, Hooper Center switched from clonidine to buprenorphine treatment for all new and returning heroin clients. This study is a retrospective chart review of subject outcomes with clonidine (n=100) versus buprenorphine (n=100). Bivariate analysis suggested few pre-treatment differences in demographic characteristics, prior health status, heroin use and consequences of use, and prior substance abuse treatment. In contrast, bivariate analysis of post-treatment variables suggested statistically significant differences in lengths of stay (LOS), psychosocial group attendance, medication expenditures, and treatment completion. Additionally, Hooper Center clinical staff reported better subject engagement in treatment and psychosocial group sessions. After adjustment for possible confounding variables using logistic regression, treatment completion was predicted by buprenorphine treatment and prior substance abuse treatment completion. Using linear regression, increased LOS was predicted by buprenorphine treatment, prior substance abuse treatment completion, and increased age. The regression-adjusted positive associations between buprenorphine and both treatment completion and LOS were of greater magnitude than the positive associations suggested in bivariate analysis.

Study limitations included restriction to heroin-dependent clients at one inpatient community treatment center in Portland. Results may not be generalizable to long-acting opiate users, to outpatient heroin detoxification clients, to rural populations, or to other metropolitan areas. Public health implications of heroin detoxification

treatment include addressing high rates of remission, facilitating access to psychosocial support during and after detoxification, and coordinating treatment for patients with comorbid conditions. Barriers to widespread adoption of buprenorphine must be addressed in order to integrate evidence-based treatment into substance abuse practice. This single site study is a good example of successful integration of evidence-based practice into a public health program.

INTRODUCTION

Background & Significance

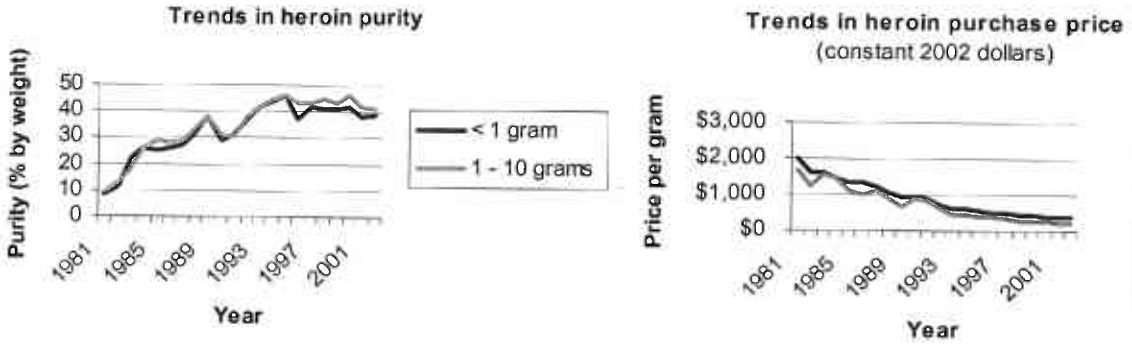
Burden of disease: United States

Heroin use is a significant and escalating public health concern in the United States. The 2002 National Survey on Drug Use and Health reported lifetime prevalence of heroin at 1.3%, up from 1% in 2000 (Substance Abuse and Mental Health Services Administration, 2001, 2003). However, the true prevalence of heroin use is probably higher because these surveys depend on respondent self-report and do not reach persons outside stable households. Although the prevalence of heroin use is relatively low compared to other health risks, the burden of disease is significant. For the user, heroin abuse is associated with job loss, arrest, and serious health conditions including fatal overdose and infectious diseases such as human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/AIDS) and hepatitis C virus (HCV) infection (Alter & Moyer, 1998; Centers for Disease Control and Prevention, 2000; McGinnis & Foege, 1999). For the community, heroin use has significant impact on decreased work productivity, increased crime, and increased health care expenditures (e.g., increased emergency department expenditures) (Mark et al., 2001; McGinnis & Foege, 1999).

In 2000, there were approximately one million chronic heroin users in the United States (Office of National Drug Control Policy, 2000). Some sources (Anthony et al., 1994) approximate that 23% of heroin users meet Diagnostic and Statistical Manual, fourth edition (DSM-IV) criteria for abuse or dependence (American Psychiatric Association, 1994; see Appendix A). However, heroin is a Schedule I Controlled Substance with high potential for abuse (Center for Substance Abuse Treatment, 2004; United States

Department of Justice, 1996); therefore risk of abuse or dependence is probably much higher. Heroin use has risen since the 1980s, due to decreased price, increased purity (see Figure 1), and increased popularity of snorting and smoking, which novices find more feasible and palatable than injection (ONDCP, 2004a; SAMHSA, 1994, 2004). Overdose is possible via any administration route. Comorbid substance use is also common among patients with a current diagnosis of opioid dependence (See Figure 2). Comorbid heroin and cocaine dependence is the most prevalent (Brooner et al., 1997).

Figure 1. Trends in heroin purity and price, 1981 – 2002



Source: ONDCP. 2004a

Figure 2. Prevalence of comorbid substance disorders among patients with a current diagnosis of opioid dependence (n=716)

Comorbid Substance Disorder	Lifetime Percentage	Current Percentage
Cocaine dependence	65	40
Cocaine abuse	12	3
Cannabis dependence	51	16
Cannabis abuse	15	2
Alcohol dependence	50	25
Alcohol abuse	13	2
Sedative-hypnotic abuse	13	2

Source: Brooner et al., 1997

Heroin users are predominantly white males, over age 30, who live in central city areas and have low socio-economic status (ONDCP, 2003). Sex as currency for heroin is an increasing trend that places users at risk for HIV and HCV infection (Garfein et al., 1996). Injection drug use has been a factor in an estimated one-third of all AIDS cases (CDC, 2000) and half of new HCV cases (Alter & Moyer, 1998) in the United States.

The societal consequences of heroin use include expenditures that otherwise would have supported legitimate spending or saving by the user. According to one national survey, in 2000, Americans spent $10 billion on heroin (ONDCP, 2001). This spending poses a significant burden for heroin-dependent persons living in poverty. For these persons coping with inadequate insurance, unemployment, homelessness, and lack of social support, heroin abuse further marginalizes them from society and makes recovery more difficult to achieve and sustain.

Burden of disease: Portland metropolitan area

In 1999, the Oregon Household Treatment Needs Study estimated that approximately 4619 (0.9%) adult residents of Multnomah County met criteria for heroin abuse or dependence (Oregon Office of Alcohol and Drug Abuse Programs, 2000). Another report, "Pulse Check: Trends in Drug Abuse", subjectively evaluates trends in select cities through a series of qualitative interviews with ethnographers/epidemiologists, treatment professionals, and law enforcement agencies. The 2004 Portland report suggested that all three respondent groups perceive heroin as the drug associated with the most serious medical, legal, and societal consequences (ONDCP, 2004b). Indeed, heroin is consistently the number one drug mentioned in Portland emergency department visits

(SAMHSA, 2004). Furthermore, in 2001, heroin (alone or in combination with other drugs) contributed to 72% of all drug-related deaths in Multnomah County (Oregon Department of State Police, State Medical Examiner Division, 2001). Heroin's legal consequences include arrests for drug-related activity and violent crime. For example, in 2003, 22% of females and 15% of males arrested in Portland tested positive for heroin (National Institute of Justice, 2004). Societal costs include heroin-related prostitution, gang-related activity, property crime, and child abuse and neglect (ONDCP, 2004b).

Treatment

There are three general phases of medical heroin treatment: (1) managed withdrawal treatment, or detoxification, for withdrawal symptom mitigation; (2) continued inpatient or outpatient treatment, for stabilization and sobriety; and (3) maintenance treatment and/or psychosocial treatment, for continued abstinence.

This study examines detoxification. When a dependent heroin user reduces or stops heroin use, subjective and objective withdrawal symptoms usually occur. Subjective symptoms include nausea, insomnia, irritability, and muscle cramps; objective symptoms include lacrimation, rhinorrhea, yawning, perspiration, and piloerection. Major withdrawal symptoms peak between 48 and 72 hours after the last heroin dose and subside after about a week (CSAT, 2004). For heavily dependent users in poor health, abrupt withdrawal can be fatal; however, heroin withdrawal is considered less dangerous than alcohol or barbiturate withdrawal.

The goal of detoxification treatment is to relieve heroin withdrawal symptoms and aid transition to long-term treatment and abstinence, which is usually combined with

behavioral and other supportive services (Bickel et al., 1997). Pharmacological treatments for heroin dependence include opioid agonists (e.g. methadone), partial opioid agonists (e.g. buprenorphine), and α_2-adrenoreceptor agonists (e.g., clonidine). All have been used for both detoxification and maintenance.

Pharmacology

Heroin (also called *acetomorphine, diacetylmorphine,* or *diamorphine)* is synthesized from morphine. After injection, or other ingestion, heroin crosses the blood-brain barrier, is converted to morphine, and binds rapidly to opioid receptors in the brain. Heroin is a mu-receptor agonist. Mu receptors are opioid receptors found mainly in the brainstem and medial thalamus, and are the key to the rewarding and addictive properties of opioids (Cox & Chavkin, 1986; Wise et al., 1986). Other full opiate agonists (e.g., methadone) compete with heroin for attachment to the mu receptor, and will elicit euphoric and analgesic opiate effects upon binding. Partial agonists (e.g., buprenorphine) also compete for mu receptor binding, but will elicit only a small degree of opiate effects. At increasing doses, partial agonists elicit increasing opiate effects until a set point at which opiate effects stop increasing or actually decrease ("ceiling effect"). Full and partial agonist medications stabilize brain neurochemistry in opiate-dependent users by replacing the short-acting opiate, heroin, with long-acting opioid. In contrast, antagonists block heroin's effect by attaching to the mu receptor, without eliciting a biological response, and blocking heroin or morphine's ability to bind (Jaffe & Martin, 1990). Appendix B provides a brief glossary of terms used in the text.

Pharmacotherapeutic options

Methadone

Methadone is the most common pharmacological agent for medically supervised detoxification to prepare for long-term methadone maintenance therapy (National Institutes of Health Consensus Panel, 1998). As an opioid and full agonist, methadone competitively binds to the mu opioid receptor and produces a long-acting, dull euphoric effect (Ward et al., 1996). As a maintenance treatment, methadone is well tolerated and effective (NIH Consensus Panel, 1998); however, the dose must be high enough to block heroin's effect (Donney et al., 2002). If the dose is too low, patients continue to use heroin and experience its euphoric effects. As a detoxification treatment, methadone is less useful. Methadone's long half-life makes it difficult to adjust dosage to patient needs and requires a long reduction period to prevent methadone withdrawal symptoms. Additionally, methadone detoxification is only available from federally regulated outpatient Opioid Treatment Programs (OTPs; i.e., methadone clinics) and from hospital emergency departments – or when a patient is admitted to the hospital for another reason. Within OTPs, clients admitted to methadone treatment must be assigned to either detoxification or maintenance at intake, which restricts treatment flexibility (Martin, 2004).

Clonidine

Clonidine is the most common treatment for acute heroin detoxification outside federally regulated OTPs (Gold et al., 1978; Gonzalez et al., 2002; Washton and Resnick, 1980), although it is not approved by the Food and Drug Administration (FDA)

for this use. Clonidine is a non-opioid, α_2-adrenergic agonist that is labeled for use as an antihypertensive. It inhibits sympathetic nerve impulses associated with heroin withdrawal, and therefore ameliorates most objective withdrawal symptoms. Clonidine has minimal risk of abuse, is not a controlled substance, has a shorter half-life than methadone, and is widely available to general physicians for outpatient treatment (Kleber et al., 1985). However, clonidine may be insufficient for managing certain subjective withdrawal symptoms – such as anxiety, restlessness, insomnia, and muscle aches (Charney et al., 1981; Cheskin et al., 1994; Jasinski et al., 1995; Washton and Resnick, 1980) – which make opiate detoxification difficult for patients. An additional limitation of clonidine is that it may induce hypotension and therefore patients require blood pressure monitoring (Gossop, 1988).

Buprenorphine

The most recent addition to the armamentarium of heroin detoxification options is buprenorphine, an opiate derived from an alkaloid extract of the opium poppy. In 2002, the FDA approved buprenorphine for the treatment of opiate dependence. Under the Drug Abuse Treatment Act (DATA) of 2000 (U.S. House of Representatives, 2000), buprenorphine is the only opioid medication available for qualified physicians to prescribe or dispense in medical offices or other settings outside federally approved OTPs. The Substance Abuse and Mental Health Services Administration requires these physicians to complete eight hours of training and to facilitate access to patient psychosocial rehabilitation services, such as counseling and vocational education.

Buprenorphine is a partial mu agonist and kappa antagonist that offers weaker opiate effects, lower risk of overdose, and easier withdrawal than full agonists (Cowan 1977; Dum and Herz, 1981; Hambrook and Rance, 1976, Lewis, 1985; Leander, 1987; Negus et al., 1989). Buprenorphine partially occupies the mu receptor with higher affinity than full agonists (e.g., heroin, methadone, and morphine) and therefore prevents those agonists from binding and activating the receptor (Cowan 1977; Dum and Herz, 1981; Hambrook and Rance, 1976; Jasinski et al., 1978). Its high affinity for and slow dissociation from mu receptors give buprenorphine a long duration of symptom relief (Lewis, 1985; Jasinski et al., 1978; Rance & Dickens, 1978). Withdrawal from buprenorphine is very mild compared with heroin withdrawal, which makes it a good candidate for both detoxification and maintenance (Bickel et al., 1988; Diamant et al., 1998; Fudala et al., 1990; Jasinski et al., 1978; Lintzeris, 2002; Mello & Mendelson, 1980).

As a partial agonist with high mu-receptor affinity, buprenorphine binds tightly to the mu receptor, but does not fully activate it. This low intrinsic activity leads to a "ceiling effect" in which higher buprenorphine doses lengthen its duration of action, but do not increase its agonist activity (Chawarski et al., 1999; Walsh et al., 1994, 1995). This ceiling effect decreases toxicity and contributes to a higher safety profile than full agonists such as methadone, which elicits significant respiratory depression at high doses (Cowan et al., 1977). In fact, it is difficult to overdose on buprenorphine, unless combined with other drugs that decrease respiration, such as benzodiazepines, alcohol, or other sedatives (Johnson et al., 2000; Kintz, 2001, 2002a, 2002b). Buprenorphine's partial agonist activity also limits its abuse potential, especially compared to methadone

(Eissenberg et al., 1996). However, potential for abuse still exists because buprenorphine's partial agonist properties can cause euphoric effects in naïve users.

At higher doses buprenorphine also blocks concurrently administered opioids (Rosen et al., 1994; Strain et al., 2002), possibly through cross-tolerance (Bickel et al., 1988) or through pharmacological antagonism in opioid-dependent clients who begin buprenorphine too soon after their last dose of heroin or methadone (Walsh et al., 1995). Buprenorphine's pharmacological antagonism in heroin-dependent clients requires careful planning of treatment initiation (CSAT, 2004). Buprenorphine administration must begin after the patient has discontinued heroin use and begun experiencing withdrawal symptoms otherwise buprenorphine will precipitate withdrawal (Bickel & Amass, 1995; Clark et al., 2002; Johnson et al., 2003; Kosten et al., 1991; Strain et al., 1995). Buprenorphine-precipitated withdrawal may cause dysphoria and cause patients to leave treatment (Walsh & Eissenberg, 2003).

To date, randomized-controlled trials have found buprenorphine to be as effective as or more effective than methadone for heroin detoxification (Bickel et al., 1988; Johnson et al., 1992; Ling, 1998; Seifert et al., 2002; Strain, 1994). Studies without concurrent comparison group (Blom et al., 1987; Jasinski et al., 1984) and laboratory-based studies (Johnson et al., 1989; Kuhlman et al., 1998) have also supported buprenorphine's effectiveness. While long-term (> 30 days) managed withdrawal using buprenorphine is generally more effective than shorter-term treatment (Amass et al., 1994; Kakko et al., 2003), there has been growing interest and support for shorter-term detoxification (Amass et al., 2004; Diamant et al., 1998; Lintzeris, 2002; O'Connor et al., 1997; Palmstierna, 2004).

In summary, buprenorphine's pharmacologic properties are unique compared to other opioid treatments and suggest that buprenorphine may be well suited for office-based treatment or non-traditional treatment settings, such as community-based inpatient detoxification centers.

Buprenorphine versus clonidine

Randomized clinical trials comparing buprenorphine and clonidine detoxification have found that, compared to clonidine clients, buprenorphine clients experience less severe subjective and objective opiate withdrawal symptoms (Lintzeris et al., 2002; Nigam et al., 1993; Oreskovich et al., 2005), experience mitigation of symptoms earlier (Cheskin et al., 1994; Nigam et al., 1993), remain in treatment longer (Lintzeris et al., 2002), and have greater success in completing detoxification (O'Connor, 1997). However, results from Nigam (1993) were limited to non-intravenous drug users, and Cheskin (1994), Nigam (1993) and O'Connor (1997) did not examine the currently preferred dosage quantities and form, sublingual buprenorphine tablets. Results from Lintzeris and colleagues' (2002) more recent evaluation of sublingual buprenorphine tables in two Australian outpatient clinics suggested superior treatment retention and less withdrawal severity for buprenorphine compared to clonidine. Using a study population most similar to that examined in the present study, Oreskovich and colleagues (2005) conducted a small, randomized-controlled pilot study in a Seattle inpatient detoxification center. Although results were limited by small sample sizes, superior outcomes with buprenorphine suggested that a larger randomized trial is warranted. It is important to point out that the Seattle study (Oreskovich et al., 2005) and the present study are the first

to compare buprenorphine to clonidine following FDA approval of buprenorphine for heroin detoxification. This study is a retrospective chart review of 200 heroin-dependent subjects who received heroin detoxification treatment at an inpatient community-based detoxification center ether before or after a center-wide switch from clonidine (n=100) to buprenorphine (n=100).

Clinical Context

This study compares clonidine to buprenorphine for heroin-dependent clients seeking voluntary treatment at David P. Hooper Detoxification Center. Hooper Center is a 24-hour community-based treatment center that primarily serves the metropolitan Portland community. It houses a 54-bed sub-acute medical detoxification unit for alcohol, opiate, and cocaine dependent clients.

Hooper Center was founded in 1973, when the Oregon legislature defined alcoholism as a disease and not a responsibility of the criminal justice system. It is managed by Central City Concern (CCC), a non-profit agency in Portland. CCC receives funding from client fees, medical insurance billing, tenant fees, private funds, state and local funds (from Multnomah Country personal income tax revenues and grants from the Oregon Department of Human Services), and federal funds (including a Collaborative Initiative award and funding from CCC's status as a Federally Qualified Health Center) (CCC, 2003).

Objectives & Hypotheses

Objective 1: To compare relative risk (RR) of treatment completion among clonidine versus buprenorphine clients who receive heroin detoxification treatment at Hooper Center.

Hypothesis 1: Buprenorphine would have greater efficacy as measured by treatment completion. Prior to study initiation, Hooper Center's medical director estimated that approximately 66% of buprenorphine clients versus 45% of clonidine clients would complete treatment (RR ≥ 1.46). This estimate was used to calculate sample size, as discussed below.

Objective 2: To compare lengths of stay (LOS) for heroin detoxification subjects who received clonidine versus buprenorphine at Hooper Center.

Hypothesis 2: Buprenorphine subjects would have longer LOS than clonidine subjects.

METHODS

Study setting

Hooper Center treats approximately 1200 opiate dependent persons each year. Until June 15, 2004, Hooper Center used a standard clonidine protocol (O'Connor et al., 1995) to mitigate opiate withdrawal symptoms. In mid-June, 2004, Hooper Center's medical director initiated a buprenorphine detoxification protocol for all new opiate dependent clients (see Appendix C). The protocol followed the "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction" (CSAT, 2004). This project used a retrospective cohort study design to compare outcomes of heroin detoxification treatment using clonidine (n=100) versus buprenorphine (n=100).

Managed withdrawal protocol

After admission and prior to dosing, clients completed questionnaires about demographics, drug use history, and substance abuse treatment history. Nurses completed client medical history interviews, physical exams, and laboratory evaluations to assess health status. These data sources are discussed further in the Data Collection section below. Clonidine was administered as an oral tablet over five to six days (0.1 mg by mouth every four hours for two days, then every six hours for one day, every eight hours for one day, and every twelve hours for two days). Buprenorphine was administered as a sublingual tablet according to the protocol outlined in Appendix C. Before admission to buprenorphine treatment, clients were required to provide a methadone-negative, benzodiazepine-negative urine sample. This precaution was taken to prevent buprenorphine-precipitated withdrawal related to an oral opioid (methadone),

and to prevent potentially fatal adverse drug reactions between benzodiazepines and buprenorphine (Kintz, 2001, 2002a, 2002b). Clients who tested positive for either of these drugs were asked to return after one day of abstinence. Clients also were required to abstain from heroin use for one day prior to admission. Per clinical guidelines (CSAT, 2004), length of buprenorphine detoxification treatment was not arbitrarily assigned at intake, but was determined by client progress and needs. A two-day induction phase was used to stabilize the client and minimize withdrawal symptoms. Buprenorphine dose was then gradually reduced over three to six days (for a total period of five to eight days). During buprenorphine treatment, nurses measured vital signs, assessed withdrawal symptoms using the Clinical Opiate Withdrawal Scale (COWS; Wesson et al., 1999), and administered extra doses as needed.

Ancillary medications

Withdrawal symptoms not relieved by clonidine or buprenorphine were treated with ancillary medications according to clients' clinical needs but within protocol dosing guidelines. These medications were used to manage anxiety and restlessness (chlordiazepoxide, hydroxyzine pamoate), bone pain and arthralgias (ibuprofen and acetaminophen), nausea (promethazine), diarrhea (loperamide, diphenoxylate), and insomnia (trazodone).

Counseling and psychosocial groups

During managed withdrawal treatment at Hooper Center, subjects were required to receive substance abuse counseling from trained addiction counselors and attend two daily

group sessions, including afternoon or evening group therapy or health education sessions, evening Narcotics Anonymous meetings, and afternoon or evening relaxation sessions. Daily acupuncture therapy was administered each morning, as stimulation of certain acupuncture loci may mitigate heroin withdrawal symptoms (Montazeri et al., 2002; Timofeev, 1999; Washburn et al., 1993).

Subject Selection

Sampling method

The clonidine cohort was selected from 100 consecutive records of Hooper Center clients admitted for heroin detoxification between October 1, 2003 through November 15, 2003 and from May 1, 2004 through June 14, 2004. Two time-periods were selected to allow examination of possible seasonal variation in length of stay, which will be evaluated in the Analysis section below. Following the center-wide switch to buprenorphine on June 15, 2004 and a phase-in period to allow for treatment administration refinement, the buprenorphine cohort was selected from 100 consecutive records of Hooper Center clients admitted for detoxification from heroin between October 1, 2004 through December 30, 2004. For logistical reasons, buprenorphine data collection was not divided between two seasons.

Eligibility criteria

Subject selection was restricted to Hooper Center clients who received either the clonidine or buprenorphine protocol to treat acute heroin withdrawal. Because this study exclusively examined heroin detoxification, clients admitted to Hooper Center for

withdrawal from any substance other than or in addition to heroin were excluded. Hooper Center's eligibility criteria are as follows; study-specific criteria are noted:

Hooper Center inclusion criteria

1. At least eighteen years old
2. American Psychiatric Association Diagnostic and Statistical Manual, fourth edition (DSM-IV) criteria for opioid dependence (DSM-IV code: 304)
3. For heroin detoxification protocol: Physically dependent on heroin; reported symptoms of opioid withdrawal and requested medical treatment for these symptoms

Hooper Center exclusion criteria

1. Evidence of acute severe psychiatric condition (e.g., active psychosis, manic-depressive illness), imminent suicidality, or serious medical illness that would have made participation medically hazardous (e.g., severe liver or cardiovascular disease)
2. Known allergy or sensitivity to buprenorphine or clonidine
3. Concurrent medication that could interact adversely with clonidine or buprenorphine
4. Pregnant or lactating
5. For this study: Physically dependent on any other substance including benzodiazepines and oral opioids (e.g., methadone)
6. For this study: Methadone or levo-alpha-acetyl-methadol (LAAM) maintenance or detoxification within thirty days of enrollment

All subjects who met eligibility requirements were used in the analysis.

Institutional Review Board approval

This study (#IRB00000305) was approved by the Oregon Health & Science University Institutional Review Board (IRB) in accordance with 45CFR46.101(b)(4), Protection of Human Subjects. This protocol is also compliant with 42CFR2, Confidentiality of Alcohol and Drug Abuse Patient Records. Finally, a letter of agreement between Central City Concern, Hooper Center's overseeing agency, and Dr. McFarland (Thesis Chair) is included in Appendix D.

Data Collection

Source

All data collected for this retrospective chart review were obtained from medical records at Hooper Center. Exposure was defined by admission date: clonidine cohort (admitted during October 1, 2003 - November 15, 2003 or May 1 - June 14, 2004), buprenorphine cohort (admitted during October 1 - December 30, 2004). If a subject was admitted during both time periods, that subject was assigned to the earlier clonidine cohort. Records from a subject's prior admission(s) to Hooper Center were used only to fill in missing demographic or prior treatment information. Collected data were de-identified, and no protected health information was collected.

Protocol

Each subject's medical chart was abstracted using a standardized procedure that audited each record for baseline demographics, prior and current heroin use, prior substance abuse treatment, medications received and psychosocial groups attended at

Hooper Center, and discharge type. Hooper Center staff arranged each chart's documents chronologically beginning with intake, as described below. Data were collected in the same order, such that discharge type was the last variable recorded.

Intake documentation

- An intake coordinator used the Vital Information Form to record each client's demographic information. Clients also completed treatment consent forms at intake. For the present study, demographic data collection was restricted to gender, race/ethnicity, age at admission, and marital status. Contact information, date of birth, and social security number were not recorded. Year of birth was used to verify reported age.
- A nurse completed the Nursing Admission Assessment to document entry date, current medications, self-reported current substance use (including last use, amount, frequency, length of current episode, and age at first use), and self-reported admission to and completion of prior substance abuse treatment. Nurses also completed a physical examination, medical history, and laboratory tests to rule out current benzodiazepine or methadone use and pregnancy.

Treatment documentation

- The administering nurse recorded each dose (date, time, and amount) of clonidine or buprenorphine and all ancillary medications.
- Counselors completed a daily checklist to record each client's attendance in morning acupuncture therapy, afternoon or evening group therapy or health education sessions, evening Narcotics Anonymous meetings, and afternoon or evening relaxation sessions.

The checklist also showed days on which a client was excused from these sessions due to illness. No psychiatric therapy or social work counseling notes were accessed.

Discharge documentation

- A nurse completed the Detoxification Summary Sheet at discharge. The nurse evaluated each client for participation in discharge planning (for continued treatment and sobriety), group participation, program cooperation, and treatment progress. This form also documented the discharge type (complete, against medical advice, incomplete, behavioral, or medical). Because the discharge summary form was physically located at the back of each admission record, each subject's discharge type was unknown to the data collector until all other data were collected.

Data quality assurance

All data were collected on-site at Hooper Center using a standardized protocol based on the forms described. Data were double entered into a password-protected Excel file, and then imported into SPSS, version 12. Discrepancies in data entry were resolved by consulting the original medical record. Although medical records included identifying information for each client, no identifying information or protected health information were collected or transported outside of Hooper Center.

Analysis Plan

Hypothesis testing

Hypothesis 1: The null hypothesis was that an equal proportion of buprenorphine and clonidine subjects would complete treatment (treatment completion RR=1). The alternate hypothesis was that buprenorphine subjects would have greater treatment completion than clonidine subjects, with RR ≥ .46. Treatment completion was defined by complete discharge as recorded on the Nursing Discharge Summary; incomplete treatment was defined as any other discharge type (i.e., incomplete, AMA, behavioral, or medical). Differences in treatment completion were analyzed using a chi-square test of statistical significance for bivariate cross-tabular analysis.

Hypothesis 2: The null hypothesis was that buprenorphine subjects' lengths of stay would not differ from those of clonidine subjects. The alternative hypothesis was that buprenorphine subjects would have longer LOS than clonidine subjects. LOS was calculated by subtracting each subject's entry date, as recorded on the Nursing Admission Assessment, from discharge date, as recorded on the Nursing Discharge Summary. Same-day discharges were counted as one day in treatment. Differences in mean LOS between groups were analyzed using an independent-samples t-test.

Definition of key analysis variables

The key independent variable was treatment group (1=buprenorphine; 0=clonidine). Key dependent variables were treatment completion (1=complete; 0=incomplete) and length of stay (continuous, with same-day discharges accruing one day).

Independent variables also included demographics, such as age at admission, gender, race/ethnicity, homelessness status (1=not homeless; 0=homeless), employment status (1=employed; 0=unemployed), marital status (1=married; 0=not currently married), and insurance status (1=insured; 0=uninsured); health status variables, such as history of psychiatric illness (1=yes; 0=no), current psychiatric illness (1=yes; 0=no), general health at admission (1=poor, 2=fair, or 3=good), self-reported Hepatitis C status as of 2000 or later (1=HCV-positive; 0=HCV-negative); substance abuse variables, such as prior treatment for heroin dependence (1=yes; 0=no), successful completion of that prior treatment (1=yes; 0=no), lifetime years of heroin use, and quantity of current heroin use; group therapy attendance variables, such as the number of days each subject was excused from groups due to illness (1=excused for > 1 day; 0=excused for ≤1 day); and prior arrest (1=yes; 0=no) or job loss (1=yes; 0=no) due to heroin use. These variables were assessed as possible confounders using bivariate and multivariate analysis.

Sample size/power considerations

Sample size was calculated to provide sufficient power to detect treatment completion RR ≥ .46. EpiInfo StatCalc version 6 (CDC, 1993) was used to estimate sample size of 100 subjects per group in order to have 80% power to detect a statistically significant difference between groups at α=.05

Statistical methods

Bivariate analysis of independent and dependent variables used chi-square tests (for categorical variables) and t-tests (for continuous variables) to examine differences

between the buprenorphine and clonidine cohorts. Logistic and linear regression analysis adjusted for confounding variables. Two-tailed statistical significance was set at $p<0.05$.

RESULTS

Bivariate analysis

Bivariate analysis suggested few differences in demographic characteristics (Table 1). In both cohorts, most subjects were male (79% of clonidine subjects versus 72% of buprenorphine subjects), over 30 (mean ± SD: 39 ± 12 versus 36 ± 11), white (80% for each group), not currently married (91% versus 80%), homeless (34% versus 35%), unemployed (94% versus 88%), and uninsured (50% versus 81%). For the continuous variable age, a t-test found no significant differences in mean age between groups at α=0.05. Chi-square test for categorical variables suggested that the only demographic characteristics that varied significantly between groups were marital status (χ^2=4.31, degrees of freedom (df)=1; p=0.04) and uninsurance (χ^2=21.09, df=1; p<0.001).

Table 1. Demographics

	Clonidine (n=100)		Buprenorphine (n=100)			
	n (%) or range	mean ± SD	n (%) or range	mean ± SD	test statistic	p-value
Male	79 (79%)		72 (72%)		χ^2=1.33	p=0.25
Age	18–62	39 ± 12	18–72	36 ± 11	t=1.75	p=0.10
Race/ethnicity					χ^2=7.40	p=0.12
White	78 (80%)		80 (80%)			
African-American	6 (6%)		5 (5%)			
Asian	0		1 (1%)			
American Indian	7 (7%)		1 (1%)			
Hispanic	7 (7%)		13 (13%)			
Marital status					χ^2=4.31	p=0.04
Married	9 (9%)		19 (20%)			
Not currently married	87 (91%)		76 (80%)			
Homeless	34 (34%)		35 (35%)		χ^2=0.22	p=0.64
Unemployed	93 (94%)		86 (88%)		χ^2=2.27	p=0.13
Uninsured	49 (50%)		81 (81%)		χ^2=21.09	p<0.001

Comparisons of prior health status also suggested no statistically significant differences between groups (Table 2). In general, subjects were in good health (65% of clonidine subjects versus 67% of buprenorphine subjects), and were HIV-negative (99% versus 97%) but HCV-positive (48% versus 46%) (self-reported status as of 2000 or later).

Table 2. Prior health status

	Clonidine (n=100) n (%)	Buprenorphine (n=100) n (%)	test statistic	p-value
Nurse assessed				
General health			χ^2=0.15	p=0.93
Good	64 (65%)	65 (67%)		
Fair	29 (29%)	26 (27%)		
Poor	6 (6%)	6 (6%)		
Self reported				
HIV-positive	1 (1%)	2 (3%)	χ^2=0.35	p=0.55
HCV-positive	35 (48%)	36 (46%)	χ^2=0.05	p=0.83
Psychiatric history				
Depression	57 (57%)	55 (56%)	χ^2=0.04	p=0.84
Anxiety	29 (29%)	29 (29%)	χ^2<0.01	p=0.96
Post-traumatic stress disorder	7 (7%)	7 (7%)	χ^2<0.01	p=1.00
Bipolar	7 (7%)	10 (10%)	χ^2=0.61	p=0.43
Schizophrenia	2 (2%)	0	χ^2=2.00	p=0.16
Suicidality	14 (14%)	24 (24%)	χ^2=3.26	p=0.07
Prior psychiatric treatment	45 (45%)	33 (33%)	χ^2=2.84	p=0.09
Current psychiatric diagnosis	26 (26%)	16 (16%)	χ^2=2.89	p=0.09
Arrived with psychiatric meds	8 (8%)	8 (8%)	χ^2<0.01	p=0.98
Received psych meds at Hooper	10 (10%)	13 (13%)	χ^2=0.48	p=0.49

Psychiatric history was similar for both groups, with a majority of subjects in each group reporting history of depression (57% versus 56%). More buprenorphine subjects self-reported a history of suicidality (14% versus 24%; χ^2=3.26; p=0.07), but the difference was not statistically significant. Similarly, more clonidine subjects self-reported receiving prior psychiatric treatment (45% versus 33%) and current psychiatric diagnosis (26% versus 16%); neither difference was statistically significant (p=0.09).

There were no differences in the percentages of subjects who arrived at Hooper Center with psychiatric meds (8% for both groups) or received psychiatric medications during their admission (10% versus 13%).

Some cohort differences were seen in self-reported heroin use, consequences of use, and prior substance abuse treatment (Table 3). All subjects reported daily heroin use (two missing data points in the clonidine group). Both groups reported daily heroin quantities that ranged from one-eighth of a gram to 5 grams. Median quantity of daily heroin use did not differ significantly between groups (0.75 grams versus 1 gram). The majority

Table 3. Self-reported heroin use, consequences of use, and prior treatment

	Clonidine (n=100)		Buprenorphine (n=100)			
	n (%) or range	mean ± SD	n (%) or range	mean ± SD	test statistic	p-value
Age at first use	12–50	24 ± 9	7–56	24 ± 9	t= -0.24	p=0.81
median (IQR)	21 (12)		22 (12)			
Lifetime use (yr.)	0–46	15 ± 12	0–55	12 ± 11	t=1.68	p=0.10
median (IQR)	10 (19)		8 (14)			
Current episode (mo.)	0–36	6 ± 7	1–180	17 ± 30	t= -3.72	p<0.001
median (IQR)	3 (6)		6 (20)			
Quantity per day (g.)	1/8–5	0.91 ± 0.78	1/8–5	1.12 ± 0.90	t= -1.75	p=0.08
median (IQR)	0.75 (0.50)		1.00 (1.00)			
Daily use	98 (99%)		100 (100%)		χ^2=1.02	p=0.31
Administration route					χ^2=2.91	p=0.41
Intravenous	79 (81%)		73 (73%)			
Intramuscular	12 (12%)		16 (16%)			
Smoke	4 (4%)		9 (9%)			
Snort	3 (3%)		2 (2%)			
Consequences of use						
Arrested (past year)	32 (33%)		36 (39%)		χ^2=0.77	p=0.38
Lost job (ever)	45 (47%)		31 (33%)		χ^2=3.60	p=0.06
Family/friend intervention	85 (89%)		68 (73%)		χ^2=7.29	p=0.01
Prior substance abuse treatment						
Attended	79 (79%)		72 (73%)		χ^2=1.07	p= 0.30
Completed	61 (61%)		47 (50%)		χ^2=2.62	p= 0.11

of subjects in both groups used heroin intravenously (81% versus 73%); intramuscular administration was more common than smoking or snorting heroin. Routes of administration did not vary between groups.

Age at first heroin use was similar between clonidine and buprenorphine groups (mean ± SD: 24 ± 9 for both groups), although range age at first use varied (12–50 years old versus 7–56). Lifetime years of heroin use ranged from less than one year to five or more decades for both groups. On average, clonidine subjects had longer lifetime use, although the difference was not statistically significant (mean ± SD: 15 ± 12 years versus 12 ± 11). However, mean duration of continuous heroin use before seeking detoxification treatment was significantly higher for the buprenorphine (mean ± SD: 17 ± 30 months) versus the clonidine (mean ± SD: 6 ± 7) cohort ($t= -3.72$; $p<0.001$). Six subjects had been using heroin continuously for more than 5 years; all were in the buprenorphine group.

Self-reported consequences of heroin use suggested some differences between groups. Cohorts did not differ in self-reported prior year arrest (33% versus 39%). However, more clonidine subjects reported they had lost a job due to heroin use (47% versus 33%, $\chi^2=3.60$, $p=0.06$) and had been pressed to seek treatment by a friend or family member (89% versus 73%, $\chi^2=7.29$, $p<0.01$).

Clonidine and buprenorphine cohorts did not differ significantly in prior substance abuse treatment attendance (79% versus 73%) or prior treatment completion (61% versus 50%).

Bivariate analysis of post-treatment outcomes suggested significant differences across all measurements (Table 4). On average, clonidine subjects remained in treatment for

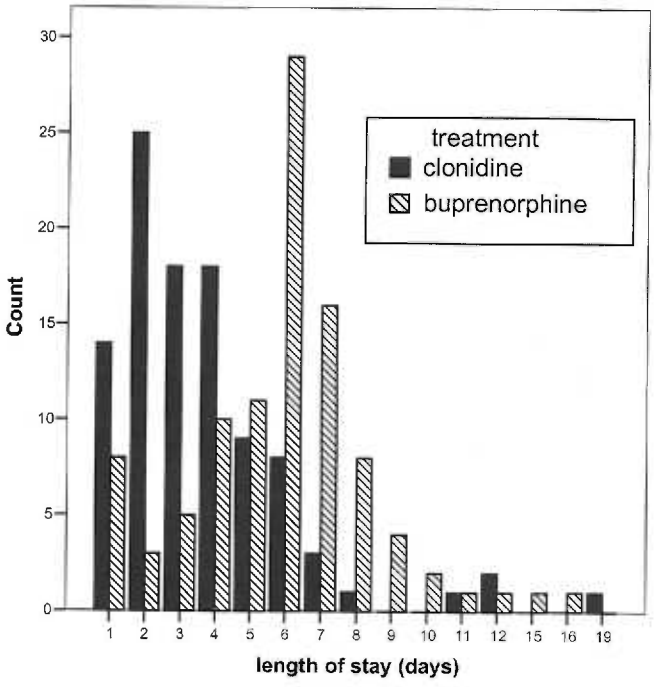
significantly fewer days (mean ± SD: 3.51 ± 2.22 versus 5.74 ± 2.46; t= -6.70, df=196; p<0.001), although range in length of stay was similar (Figure 3). For subjects who completed treatment, mean LOS was also significantly shorter for clonidine versus buprenorphine subjects (mean ± SD: 5.04 ± 2.21 days versus 7.03 ± 1.72; t= -5.32, df=109; p<0.001)]. There was no difference in length of stay between clonidine clients admitted during the fall versus spring season (mean ± SD: 3.44 ± 2.25 days versus 3.58 ± 2.20).

Groups were also compared for attendance in psychosocial therapy. As a group, clonidine subjects attended fewer sessions than buprenorphine subjects. Significantly more clonidine subjects were excused from more than one day of group therapy due to illness (80% versus 26%). More buprenorphine subjects attended multiple days of

Table 4. Heroin detoxification treatment outcomes

	Clonidine (n=100)		Buprenorphine (n=100)			
	n (%) or range	mean ± SD	n (%) or range	mean ± SD	test statistic	p-value
Length of stay (days)	1–12	3.51± 2.22	1–15	5.74 ± 2.46	t= -6.70	p<0.001
Group attendance > 1 day						
Acupuncture	62 (62%)		85 (86%)		χ^2=14.67	p<0.001
Narcotics Anonymous	60 (60%)		90 (91%)		χ^2=28.40	p<0.001
Relaxation	23 (23%)		60 (61%)		χ^2=25.61	p<0.001
Other groups	57 (58%)		89 (90%)		χ^2=26.71	p<0.001
Excused > 1 day	80 (80%)		26 (26%)		χ^2=57.71	p<0.001
Medication expenditures						
All medications	$0.97–19.53	$7 ± $4	$0.27–59.08	$31 ± $1	t= -20.34	p<0.001
Ancillary medications	$0.50–18.51	$6 ± $3	$0–$10.34	$2 ± $2	t=10.07	p<0.001
Discharge evaluation, average or better (scale: none–excellent)						
Discharge planning	48 (50%)		73 (73%)		χ^2=11.49	p=0.001
Group participation	51 (53%)		79 (79%)		χ^2=15.32	p<0.001
Program cooperation	48 (50%)		80 (80%)		χ^2=20.42	p<0.001
Treatment progress	43 (44%)		58 (60%)		χ^2=4.31	p=0.04
Discharge type					χ^2=8.97	p=0.03
Complete	46 (46%)		67 (67%)			
Incomplete	54 (54%)		33 (33%)			

Figure 3. Length of stay: clonidine versus buprenorphine



therapy sessions, including acupuncture (62% versus 86%); group therapy (20% versus 74%); Narcotics Anonymous (60% versus 91%); relaxation (23% versus 61%); and other groups such as HIV education (58% versus 90%). All group attendance differences were significant at $p<0.001$.

Medication expenditures also differed significantly between groups. On average, total medication expenditures were substantially less for the clonidine versus buprenorphine cohorts (mean ± SD: \$7.92 ± \$3.88 versus \$30.57 ± \$1.04; t= -20.34; $p<0.001$). However, total expenditures on medications used to treat symptoms not relieved by, or side effects of, clonidine or buprenorphine were significantly more for the clonidine cohort (mean ± SD: \$6.09 ± \$3.30 versus \$2.21 ± \$1.98; t=10.01; $p<0.001$).

Discharge records completed by as nurse suggested that subjects in the clonidine cohort received lower scores than buprenorphine subjects on scales that rated discharge planning, group participation, program cooperation, and treatment progress. All differences were significant at p=.04 or less.

Finally, clonidine subjects were significantly less likely to complete heroin detoxification treatment compared to buprenorphine subjects (46% versus 67%; χ^2=8.97; p=0.03; RR=1.46, 95% CI: 1.14, 1.87).

Multivariate analysis

Multivariate logistic regression analysis of treatment completion and linear regression analysis of length of stay were performed to adjust for confounding variables. To construct each model, SPSS stepwise conditional analysis was used first to examine variables that approached statistical significance in bivariate analysis. Variables that did not contribute significantly to the model [i.e. Wald scores (for logistic regression) or t-scores (for linear regression) not statistically significant at p=0.10)], those with very small cell counts, and those redundant to more robust variables were considered unlikely confounders and excluded from further analysis. Following these exclusions, variables of interest were further examined for clinical and statistical significance using manual (i.e., not "canned") stepwise analysis in SPSS.

In the final logistic model (Figure 4), treatment completion was predicted by treatment group and completion of prior substance abuse treatment. The Hosmer and Lemeshow goodness-of-fit test was not statistically significant (χ^2=1.06, df=2; p=0.59). Therefore we fail to reject the null hypothesis that there is no difference between the

Figure 4. Logistic regression of treatment completion

Covariate	β	S.E.	Wald	df	Sig.	Exp(β)	95% Confidence Interval for exp(β)	
							Lower	Upper
Constant	-0.66	0.28	5.40	1	p=0.02	0.52		
treatment group	0.96	0.31	9.84	1	p=0.002	2.62	1.44	4.79
completed prior substance abuse treatment	0.80	0.31	6.75	1	p=0.009	2.22	1.22	4.06

Dependent variable: treatment completion
* No outliers found.

Model: $\text{logit}(y) = 0.52 + 2.62x_1 + 2.22x_2$

where: y = discharge type (1=complete; 0=incomplete)

x_1 = treatment group (1=buprenorphine; 0=clonidine)

x_2 = completed prior substance abuse treatment (1=yes; 0=no)

observed and predicted values of treatment completion, which implies that the model's estimates reasonably fit the data. DFBetas and Cook's test did not identify any influential cases (outliers). The model suggests that, after adjusting for all other covariates including prior treatment completion, buprenorphine subjects were 2.6 times more likely to complete treatment than clonidine subjects (OR=2.62, 95% CI: 1.44, 4.79; p=0.002).

Construction of the linear model for length of stay required an additional stage of analysis following identification of several outliers. First, using all cases, the LOS model included treatment group, current psychiatric diagnosis, prior substance abuse treatment completion, and age (F=15.05, df=4; p<0.001) (Figure 5). However, casewise diagnostics identified three influential cases in which the residual was more than 3 SD greater than the predicted value; in these cases LOS was more than 14 days. When these 3 outliers were excluded from analysis, the variable for current psychiatric diagnosis no longer contributed significantly to the model. In the final linear model (F=21.14, df=4; p<0.001), holding all other covariates constant, buprenorphine treatment lengthened LOS by 2.45 days (95%

CI: 1.80, 3.11; p<0.001) compared to clonidine; having completed prior substance abuse treatment lengthened LOS by 1.03 days (95% CI: 0.37, 1.70; p=0.003); and each 10-year increase in age lengthened LOS by 0.4 days (95% CI: 0.1, 0.7; p=0.01).

Figure 5. Linear regression of length of stay (LOS)

Covariate	Unstandardized Coefficients		t	Sig.	95% Confidence Interval for β	
	β	Std. Error			Lower Bound	Upper Bound
Constant	0.66	0.71	0.93	p=0.35	-0.74	2.05
treatment group	2.63	0.37	7.11	p<0.001	1.90	3.36
completed prior substance abuse treatment	1.09	0.37	2.94	p=.004	0.36	1.83
age	0.05	0.02	3.13	p<0.001	0.02	0.09
current psychiatric diagnosis	1.20	0.45	2.68	p=.002	0.31	2.08

Dependent variable: length of stay

Model: $y = 0.66 + 2.63\ x_1 + 1.09x_2 + 0.05x_3 + 1.20x_4$

where: y = discharge type (1 = complete; 0 = incomplete)

x_1 = treatment group (1 = buprenorphine; 0 = clonidine)

x_2 = completed prior substance abuse treatment (1 = yes; 0 = no)

x_3 = age (continuous, by year)

x_4 = current psychiatric diagnosis (1 = yes; 0 = no)

Casewise diagnostics identified three outliers above three standard deviations. These three influential cases were then excluded from analysis to find the best fit model:

Covariate	Unstandardized Coefficients		t	Sig.	95% Confidence Interval for β	
	β	Std. Error			Lower Bound	Upper Bound
Constant	1.41	0.64	2.20	p=0.03	0.15	2.66
treatment group	2.45	0.33	7.36	p<0.001	1.80	3.11
completed prior substance abuse treatment	1.03	0.34	3.09	p=.002	0.37	1.70
Age	0.04	0.02	2.53	p=0.01	0.01	0.07

Model excluding outliers: $y = 1.41 + 2.45\ x_1 + 1.03x_2 + 0.04x_3$

where: y = discharge type (1 = complete; 0 = incomplete)

x_1 = treatment group (1 = buprenorphine; 0 = clonidine)

x_2 = completed prior substance abuse treatment (1 = yes; 0 = no)

x_3 = age (continuous, by year)

DISCUSSION

Key Findings

Prior to June 15, 2004, Hooper Detoxification Center used clonidine to treat clients seeking managed heroin withdrawal. On that date, Hooper Center began using buprenorphine exclusively to treat all new and returning clients. This protocol change provided a natural experiment to compare the effectiveness of these two heroin detoxification treatments. A sample of 100 consecutive medical charts was obtained for both clonidine and buprenorphine cohorts. Demographic analysis suggested that, prior to treatment, the two groups were very similar in distributions of gender, age, race/ethnicity, homelessness, and unemployment status. Significantly more buprenorphine subjects were currently married, which may be related to the recent observation that more heroin users in Portland are reporting to treatment as couples (ONDCP, 2004b). Significantly more buprenorphine subjects were also uninsured. This finding may be related to recent legislative changes in which Medicaid funds for outpatient chemical dependency were cut from the Oregon Health Plan standard benefit packages, and men over age 18 were generally excluded from Medicaid coverage.

Prior to treatment at Hooper Center, clonidine and buprenorphine subjects also were similar with regard to health status. In general, they were in good health, were HIV-negative but were HCV-positive. Many subjects reported histories of psychiatric illness, but no cohort differences were noted. History of depression was noted in a majority of subjects in both groups. Anxiety, post-traumatic stress disorder (PTSD), bipolar disorder, and schizophrenia were less common. Comorbid substance abuse and psychiatric disorders are discussed in a later section. Prior psychiatric treatment was common in both groups,

and approximately half of subjects with prior psychiatric treatment had current psychiatric diagnoses. Differences in self-reported history of suicidiality approached statistical significance, with more buprenorphine subjects reporting prior suicide attempts. These differences are difficult to explain but may reflect an influx of more troubled heroin users, following Hooper Center's switch to buprenorphine. Subjective reports from the center's nursing and counseling staff noted a "buzz on the streets" that seemed to prompt new clients who may not have sought treatment previously under the clonidine protocol. This difference may reflect some changes in the client population following the center-wide switch to buprenorphine; this possibility will be discussed further.

Ages at first heroin use and lifetime years of heroin use were similar for clonidine and buprenorphine subjects. However, buprenorphine subjects reported mean duration of continuous heroin use almost three times longer than clonidine subjects. Like the suggested difference in suicidality, the difference in current duration of use may reflect client population changes. All subjects reported daily heroin use and most reported intravenous use. Quantity of daily heroin use was similar and averaged approximately 1 gram per day for both cohorts. Quantity of heroin use was not associated with either length of stay in detoxification treatment or treatment completion.

Subjects' self-reported consequences of use varied slightly. Past-year arrest did not differ, but more clonidine subjects reported they had previously lost a job due to their substance use. Although significantly more clonidine subjects reported that family members or friends had urged them to seek treatment for heroin use, both groups reported high percentages of family or friend intervention. Any differences in self-reported consequences of heroin use may be due to chance, although it is possible that

buprenorphine subjects may have been more self-motivated after a long episode of heroin use or after hearing the "buzz on the streets". Finally, although similar majorities of subjects reported attending prior substance abuse treatment, slightly more clonidine subjects reported prior substance abuse treatment completion. Completion of prior substance abuse treatment was not high in either group, and may reflect inadequate follow-up care to promote long-term abstinence. This is discussed further in the section on relapse.

During treatment, subjects' attendance in psychosocial groups and acupuncture therapy suggested better treatment participation among buprenorphine subjects. Clients were only excused if they were too ill to attend. In general, clonidine subjects required more than one day of rest before they were well enough to attend group sessions. In contrast, many buprenorphine subjects were able to attend groups on the first day of treatment. Subjective staff reports noted that buprenorphine clients generally felt better throughout treatment and were able to participate actively in group sessions.

As a group, buprenorphine subjects also had significantly longer lengths of stay (LOS) than clonidine subjects, even among those who completed treatment. Results from linear regression on LOS are addressed below.

One disadvantage of buprenorphine is that it is more expensive per dose than clonidine. Average medication expenditures were almost four times higher for buprenorphine subjects. However, average medication expenditures for ancillary medications used to treat symptoms not relieved by, or side effects of, clonidine or buprenorphine were almost three times higher for clonidine subjects. Most clonidine subjects required multiple daily doses of ancillary medications; and these drugs made up

the majority of total medication expenditures for this group. In contrast, buprenorphine subjects' withdrawal symptoms were generally managed by buprenorphine itself, such that subjects did not require nearly as much medication for pain, nausea, or insomnia. Additionally, staff reported increased appetite and food intake among buprenorphine clients, which they attributed to improved treatment experience as compared to previous clonidine clients.

At discharge, a nurse evaluated each subject for participation in discharge planning (for continued treatment and sobriety), group participation, program cooperation, and treatment progress. Buprenorphine subjects performed significantly better on all scales, which suggests better overall treatment participation and progress.

Finally, buprenorphine subjects were significantly more likely to complete treatment than clonidine subjects. More than two-thirds of buprenorphine subjects, versus less than half of clonidine subjects, completed treatment. The clonidine proportion is similar to that from a nationwide survey of 25,643 opiate detoxification client admissions in 18 states, which found 49% completion (SAMHSA, 2004c).

Multivariate logistic regression identified two variables that significantly contributed to increased likelihood of treatment completion: buprenorphine treatment and prior substance abuse treatment completion. After adjusting for covariates significant in bivariate analysis, and holding those covariates constant, buprenorphine treatment predicted more than two-fold increased odds of treatment completion. The positive association between prior substance abuse treatment completion and increased treatment completion underscores issues of relapse in this population, which will be discussed later.

Multivariate linear regression identified three variables that significantly contributed to increased length of stay. After adjusting for covariates significant in bivariate analysis, and holding those covariates constant, buprenorphine treatment increased LOS by more than two days, prior substance abuse treatment completion increased LOS by one day, and each 20-year increase in age increased LOS by slightly less than one day. The treatment group effect is consistent with buprenorphine subjects experiencing more comfortable detoxification and therefore staying in treatment longer. However, increased LOS for buprenorphine subjects may suggest that subjects seeking detoxification from heroin require longer treatment periods with buprenorphine than have been generally used with clonidine. Increased LOS associated with prior substance abuse treatment completion may signal increased intent to complete current treatment. Increased LOS with age may suggest that older subjects needed more time to complete treatment, or that younger subjects had less patience with detoxification duration and possibly more desire to return to use. Alternatively, these slight increases in LOS due to age or to prior treatment completion may not be clinically significant.

In general, clients who complete opiate detoxification stay in treatment for a median of 6 days (SAMHSA, 2004c). However, heroin patients historically have had shorter LOS than alcohol and cocaine patients, possibly due to inadequate heroin treatment options (Jonkman et al., 2005). With current increases in prevalence of heroin dependence, decreased price, and increased purity, newer pharmacotherapy options, such as buprenorphine, warrant further research (McCarty et al., 2000).

Study Limitations

This study is limited by its subject sample from one voluntary inpatient community treatment center, which primarily serves uninsured persons, many of whom are homeless. As such, Hooper Center clients may not represent primary care patients, who are more likely to have insurance and social support, which are associated with better treatment outcomes (Brown et al., 2004; Schottenfeld et al., 2000).

A second limitation is the study site's location in metropolitan Portland, which may not represent substance abuse treatment options or user populations in rural areas or in other metropolitan areas outside Oregon. Additionally, Portland's history of progressive approaches to public health – for example, clean syringes are easily available without prescription – may contribute to this limitation.

A third limitation is this study's exclusive focus on heroin clients, rather than on opiate clients more generally. However, long-acting opiates, such as methadone and pain pills such as oxycodone, may elicit more difficult withdrawal, possibly due to pharmacologic differences in half-life, although the mechanism is not well understood (Johnson et al., 2003). The present study design was chosen to optimize internal validity by restricting subjects to heroin-dependent clients. Additionally, by restricting eligibility criteria, this study sought external generalizability of results to the general population of heroin users seeking detoxification.

Finally, this study may be limited by differences in patient populations before and after Hooper Center switched to buprenorphine treatment. Although the majority of pre-treatment measures did not differ between groups, buprenorphine subjects may have been more self-motivated to initiate, and possibly to complete, treatment than clonidine subjects.

Perhaps more importantly, as a group, buprenorphine subjects had been continuously using heroin longer than clonidine subjects. It is possible that many buprenorphine subjects had relapsed following prior clonidine treatment, and therefore had not sought further treatment at Hooper Center until they heard about the new detoxification drug. Study design precluded analysis of relapse rates.

Implications for Public Health

Relapse

Remission and resumption of use will continue to thwart recovery from heroin dependence. The majority of opioid-addicted persons relapse to opioid addiction after withdrawal, regardless of the treatment method used (Gossop et al., 1989; Sees et al., 2000). For example, in a 33-year follow-up of opiate-dependent patients, five years of abstinence reduced likelihood of relapse, but a substantial proportion relapsed after five years of abstinence (Hser et al., 2001). It is important to reiterate that detoxification is only one phase of heroin dependence treatment. Without referral to long-term maintenance and psychosocial support, motivation to abstain from heroin wanes and relapse is high (Mattick & Hall, 1996; NIH Consensus Panel, 1998; O'Connor & Fiellin, 2000). However, in community detoxification centers like Hooper Center, which are the primary treatment settings for homeless and uninsured clients, it is difficult to assure access to ongoing pharmacologic and behavioral therapy.

Comorbid conditions

HIV and HCV infection

Comorbid HIV and HCV infection are associated with intravenous heroin use. To date, there has been limited research on the interaction between HIV status, HIV treatment, and heroin treatment. Some studies have shown successful use of buprenorphine in HIV-positive patients (Montoya et al, 1995), including reduced HIV risk behaviors such as needle-sharing (Marsch et al., 1999) and increased adherence to highly active antiretroviral therapy (HAART) (Moatti et al., 2000). However, because HIV protease inhibitors inhibit an enzyme required for buprenorphine metabolism (Iribarne et al., 1997; Kobayashi et al., 1998), more research is needed to examine possible interactions between buprenorphine and antiretroviral therapy and to facilitate integration of collaborative treatment (Forum for Collaborative HIV Research, 2005). The present study reported very few HIV-infected Hooper Center clients. This finding may be related to the relatively low prevalence of HIV in Portland. Some clinicians have noted that Portland may have missed the initial HIV epidemic among intravenous drug users due to Portland's progressive approach to its substance abuse problem (J. Boverman, personal communication). As mentioned earlier, Portland is relatively unique in that injection drug users may purchase needles without a prescription, which improves access to clean needles and promotes disease prevention.

In contrast to the relatively low numbers of HIV-infected Hooper Center clients in this sample, half of all subjects were HCV-positive. The health burden of HCV among these clients is troubling but not surprising, as injection drug use has been associated with half of new HCV cases in the United States (Alter & Moyer, 1998). Because buprenorphine is metabolized by the liver and may worsen liver function in HCV patients

(McQuay & Moore, 1995; Petry et al., 2000; Berson et al., 2001), clinical guidelines suggest that liver function tests should be consistently monitored in these patients, especially among outpatient clients at risk of diversion to intravenous buprenorphine use (CSAT, 2004).

Psychiatric disorders

Opioid addiction is often associated with psychopathology. For example, Brooner et al. (1997) found 47% lifetime prevalence and 39% current prevalence of psychiatric disorders among 716 opioid-dependent patients after one month of stabilized substance abuse treatment. Similarly, in a study of 533 opioid-dependent patients, Rounsaville et al. (1982) found 87% lifetime prevalence and 70% current prevalence of comorbid psychiatric disorder. It is difficult to determine whether psychiatric disorders increase risk of opioid dependence or vice versa, or how other factors contribute to comorbidity in different individuals. Substance abuse can imitate or activate psychiatric symptoms (CSAT, 2004). In this study, the majority of subjects reported history of depression, and many reported prior psychiatric treatment. Comorbid psychiatric disorders may be over-reported or under-reported in this sample, due to correlation with substance abuse, inconsistent self-report and insufficient data (psychiatric records were not accessed, in accordance with subject confidentiality)

Barriers to buprenorphine adoption

Two recent federal initiatives have provided opportunities for widespread integration of buprenorphine into standard medical treatment (Fiellin & O'Connor, 2002;

Forum for Collaborative HIV Research, 2005). First, the DATA 2000 Act (U.S. House of Representatives, 2000) expanded substance abuse treatment beyond traditional federally regulated methadone clinics. Under DATA 2000, physicians may obtain a waiver to prescribe and dispense buprenorphine in outpatient (office-based) and community treatment settings. Second, administrative responsibility for treatment using opioid medications was transferred from the FDA to the Substance Abuse and Mental Health Services Administration, to increase focus on clinical outcomes rather than inspection-oriented oversight (Federal Register, 2001).

Despite these initiatives, widespread buprenorphine adoption continues is still limited by issues in financing, legislation, and social and clinical attitudes. The health care financing system includes complex relationships between Medicare and Medicaid, federal substance abuse block grants, state funds, and private insurance companies. Some private medical insurance plans cover substance abuse treatment, but many do not promote these programs in order to minimize high-risk enrollees who increase health plan expenditures. In the public health care financing system, Medicare fee-for-service coverage does not include outpatient buprenorphine prescriptions; and Medicare health maintenance organization (HMO) coverage is only available to persons whose HMOs have substance abuse and pharmacy benefits (SAMHSA, 2004). Medicaid financing depends on state allocations and federal matching contributions, such that changes in state allocation significantly effect total Medicaid funding. The Oregon Health Plan adjusts its service coverage and beneficiary enrollment to meet Medicaid funding changes. When funds are plentiful, more services are covered, including prescription drug coverage for substance abuse, and more persons are eligible for enrollment, beyond required coverage for pregnant

women, children, and women with dependent children. When funds wane, as in recent years, services are cut and enrollment is limited. These changes greatly impact publicly funded substance abuse treatment centers, such as Hooper Center. Recent Medicaid cuts resulted in staff layoffs (CCC, 2004) and elimination of medication funding. Greater prevalence of uninsurance and corresponding lack of substance abuse treatment create greater need for and burden on community-based centers with limited funding like Hooper Center and solo practitioners who must bear financial burden alone.

Legislative barriers to widespread buprenorphine adoption include a 30-patient maximum for all individual clinicians and groups who provide buprenorphine detoxification or maintenance treatment. Kaiser Permanente has been working nationally to overturn this limit (Health Resources and Services Administration, 2004), and the Senate recently passed such a bill (U.S. Senate, 2004), but it is currently stalled in the House.

Although buprenorphine has been approved for opiate treatment since 2002, few physicians are using it. In mid-2003, Join Together polled 419 SAMHSA-registered physicians on barriers to widespread buprenorphine use (Join Together, 2003). Thirty-three percent were not currently using buprenorphine. Barriers included cost, lack of insurance coverage, 30-patient limit, and inadequate pharmacy supply.

In a larger context, it is important to examine systemic barriers to the diffusion of any new substance abuse treatment. While most new pharmacotherapies are adopted quickly in general medicine – sometimes through direct-to-consumer marketing – substance abuse treatment diffusion is slower and less predictable (Thomas & McCarty, 2004). Barriers may include inadequate links between primary care and psychosocial services; inadequate translation of positive research findings into evidence-based practice;

and insufficient organizational and administrative support (Thomas & McCarty, 2004). In order for any new substance abuse treatment to achieve widespread clinical use, clinicians, staff members, and key decision-makers must be convinced of its effectiveness and promote its use, and sufficient and consistent funding must be available (Ling et al., 2004; Thomas et al., 2003).

In a National Institute on Drug Abuse (NIDA) Clinical Trials Network project, Amass and colleagues (2004) trained primary care providers in twelve community treatment programs nationwide to use and successfully integrate buprenorphine/naloxone detoxification and maintenance in their existing programs. In a similar initiative, the Opiate Medication Initiative for Rural Oregon Residents (OMIROR) trained seventeen rural physicians to use buprenorphine in their addiction treatment practices (McCarty et al., 2004). Training focused on clinical education about buprenorphine and on development of local treatment protocols. These initiatives illustrate that structured education is a key tool for changing negative attitudes among clinical providers and staff (Amass et al., 2004; McCarty et al., 2004). Because clinic resources and needs vary widely, it is important to consider these in program design. Indeed, individual program adoption of buprenorphine is probably the best diffusion route. The present project is a single site study of an organizational mandate for buprenorphine adoption. Dr. Thayer, Hooper Center's medical director, was willing to work with clinical staff and administrators to bring buprenorphine treatment to practice. Almost one year after the center-wide change from clonidine to buprenorphine, Dr. Thayer and his staff say, "There's no way we're going back."

Future Research

More research is needed to evaluate office-based buprenorphine treatment, which has the potential to increase access, reduce stigma, and facilitate treatment coordination with other medical conditions (Fudala et al., 2003; NIH Consensus Panel, 1998; Rounsaville & Kosten, 2000; Schnoll, 2001). In particular, a newer single-dose depot buprenorphine formulation shows promise as an effective detoxification medication with gradual onset, sustained release, and minimal withdrawal symptoms (Sobel et al., 2004). Widespread adoption of office-based substance abuse treatment may help shift the focus to substance abuse as a chronic condition. In turn, integration into mainstream medicine may promote better treatment options, increase insurance coverage, and foster better outcomes (Bodenheimer et al., 2002; McLellan et al., 2000). However, office-based treatment may not be practical for patients with comorbid dependence on other drugs, comorbid psychiatric disorders, and those with high risk for relapse. Additionally, indigent and under- or uninsured persons may have difficulty obtaining and maintaining access to office-based treatment.

Summary and Conclusions

This retrospective study examined outcomes for 200 subjects following a heroin detoxification protocol change from clonidine to buprenorphine. Results suggested that buprenorphine promoted superior treatment retention and treatment completion compared to clonidine. Although the buprenorphine protocol incurred higher medication expenditures, reduced need for ancillary medications and increased treatment participation and progress among buprenorphine subjects suggested better patient

withdrawal experiences. This single site study is a good example of successful integration of evidence-based practice into public health programs.

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Appendix A. American Psychiatric Association Diagnostic and Statistical Manual, fourth edition (DSM-IV) criteria for substance abuse and dependence

1. DSM-IV criteria for substance abuse

One or more of the following, occurring within a 12-month period:

1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household).
2) Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use).
3) Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct).
4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights).

2. DSM-IV criteria for substance dependence

Three of more of the following, occurring at any time in the same 12-month period:

1) Tolerance, as defined by either of the following:
   - The need for markedly increased amounts of the substance to achieve intoxication or desired effects.
   - 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.
   - The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3) Taking the substance often in larger amounts or over a longer period than was intended.
4) A persistent desire or unsuccessful efforts to cut down or control substance abuse.
5) Spending a great deal of time in activities necessary to obtain or use the substance or to recover from its effect.
6) Giving up social, occupational, or recreational activities because of substance use.
7) Continuing the substance use with the knowledge that it is causing or exacerbating a persistent or recurrent physical or psychological problem.

Source: American Psychiatric Association, 1994

Appendix B. Glossary of terms

Addiction

A behavioral syndrome characterized by repeated, compulsive seeking or use of a substance (often, but not always, accompanied by dependence, withdrawal, and tolerance)

Affinity

strength with which a drug binds to its receptor

Agonist

a chemical substance (as a drug) capable of combining with a receptor on a cell and initiating the same reaction or activity typically produced by the binding of an endogenous substance

Antagonist

a chemical that acts within the body to reduce the physiological activity of another chemical substance; especially one that opposes the action on the nervous system of a drug or a substance occurring naturally in the body by combining with and blocking its receptor

Buprenorphine

an opioid partial agonist used to treat opiate withdrawal symptoms; the only opioid medication approved for prescription and dispensing in clinical settings outside the Opioid Treatment Program setting

Buprenorphine/naloxone

a combination treatment for opioid dependence; naloxone is an opioid antagonist that is added to buprenorphine therapy to prevent diversion of medication to intravenous use

Clinical Opioid Withdrawal Scale (COWS)

used clinically to assess opiate withdrawal symptoms to determine appropriate time to begin withdrawal treatment, or to adjust medication dosage

Clonidine

an α_2-adrenoreceptor agonist used to treat opiate withdrawal symptoms (off-label use)

Dependence

a characteristic set of withdrawal signs and symptoms upon reduction or cessation of substance use

Dissociation

a measure of the uncoupling of a drug from its receptor

Drug Addiction Treatment Act of 2000 (DATA 2000)

Title XXXV of the Children's Health Act of 2000; establishes a waiver authority for qualifying physicians to prescribe or dispense specifically approved Schedule III, IV, and V opioids for the treatment of opiate dependence in clinical settings

Heroin

a strongly physiologically addictive, full opioid agonist used illicitly for its euphoric effects

Intrinsic activity

the degree to which a drug activates its receptors

Managed withdrawal treatment

detoxification treatment; used to mitigate opiate withdrawal symptoms and prepare the patient for acute treatment (stabilization and sobriety), followed by maintenance therapy with or without psychosocial support

Methadone

a full opioid agonist approved for use in the treatment of opiate addiction within federally regulated Opioid Treatment Programs

Mu opioid receptor

a receptor on the surface of brain cells that mediates opioid analgesia, tolerance, and addiction through drug-induced activation (Kappa receptors are also opioid receptors)

Opiate

a drug containing or derived naturally from opium (e.g., heroin, morphine)

Opioid

a synthetically produced drug that possesses properties characteristic of opiates, but is not derived from opium (e.g., methadone, oxycodone)

Opioid full agonist

a drug that competitively binds and activates opioid cell receptors, especially mu receptors (e.g., heroin, methadone, morphine); repeated administration often produces dependence

Opioid partial agonist

a drug with properties of both agonists (activate opioid receptors) and antagonists (block opioid receptors); the mu agonist properties of partial agonists (e.g., buprenorphine) reach a maximum at a certain dose and do not continue to increase with increasing doses ("ceiling effect"), which limits the abuse potential and side effects of opioid partial agonists

Psychosocial

therapy that combines psychological and social (e.g., occupational, recreational) aspects

Tolerance

a physiological response in which repeated substance use has diminished effect, and doses must be increased to achieve desired effect

Appendix C. Buprenorphine protocol for heroin withdrawal

Multnomah County Health Department

Hooper Center for Alcohol and Drug Intervention

Sub-acute Program

NARCOTIC WITHDRAWAL

Protocol: #202

Prepared by: Jim Thayer, MD

Date: 7/18/04; Next review date: 7/06

SUBJECTIVE:

- Drugs taken, route, dosage, duration of habit, most recent use
- Severity of past withdrawal
- Current medications
- History of hypertension, heart disease, renal disease, liver disease
- Possible pregnancy
- Symptoms of withdrawal: cramps, malaise, vomiting, diarrhea, insomnia

OBJECTIVE:

- Vital signs
- Needle sites (marks, abscesses, scars)
- Presence or absence of jaundice
- Signs of withdrawal: dilated pupils (> 2mm greater than examiner's pupils), tachycardia, gooseflesh, tremors, yawning, lacrimation, sweating, anxiety, GI upset, aches

ASSESSMENT AND PLAN:

- Patients admitted for opiate withdrawal will be assessed with the Clinical Opiate Withdrawal Scale (11-item scale to assess subjective and objective withdrawal symptoms [Wesson et al., 1999]). The COWS and vital signs will be done on opiate clients at each med pass until the COWS is > 14 and buprenorphine is started. After buprenorphine is started, vital signs will be done q12h with each buprenorphine dose. More frequent vital signs are not needed unless there are other reasons such as fever or hypertension. Once buprenorphine is started, the COWS does not need to be repeated unless clients are

continuing to complain of persistent withdrawal symptoms. Patients may receive medications for specific complaints according to protocols for insomnia, GI upset, etc.

- When COWS is >14, patients will be started on buprenorphine 4mg sublingual q12 hours times 4 doses.
- If COWS is >14 between the first four doses, an extra 4mg will be given, then the schedule is resumed.
- After the four scheduled doses of 4mg, 2mg is given q 12h times 4 doses. If the COWS is > 14 between the four doses, an extra 2mg will be given, then the schedule resumed. After the four scheduled doses of 2mg, a final 2mg dose is given 24hrs later.
- For the average patient using ½ to 2 grams of heroin/day, the above schedule has been shown to work quite well. The initial dose of buprenorphine will usually be given between 18 and 30 hours after the last heroin usage.
- Clients will be assessed for initiation of buprenorphine at each med pass except the 4pm to avoid giving the second dose at 4am. Once buprenorphine is initiated clients will be dosed as close to q12 as is practical, given the limitations of the timing of med passes.
- The initial dose of buprenorphine will need to be directly observed by a nurse or sub-acute technician trained by the nurse.

Appendix D. Letter of agreement from Central City Concern

CENTRAL CITY CONCERN

Providing Pathways to Self-Sufficiency

PORTLAND ALTERNATIVE HEALTH CENTER

December 7, 2004

Dear Dr. McFarland,

Central City Concern is pleased to cooperate with your proposed project, "Buprenorphine versus clonidine for the treatment of opiate withdrawal: a retrospective cohort study." We understand that the project will extract and analyze de-identified clinical data from archived medical records at David P. Hooper Detoxification Center, in accordance with the study protocols. In cooperation with our requirements, Anne Kovas has already signed a confidentiality agreement on site at Hooper Detoxification Center. We are interested in the outcomes of this project and look forward to working with your research team.

Sincerely,

Wendy Callander, MD
Medical Director
Central City Concern Health Services

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