

Low Dose Protocol for the Use of Buprenorphine and Suboxone®

Executive Summary

The pervasiveness of opiate and heroin addiction in Ohio has hit epidemic proportions. From 1999 to 2008, Ohio's unintentional poisoning death rate increased by 350 percent. Nearly all of those deaths have been due to drug and medication-related poisonings. Opioids, used as pain relievers (such as oxycodone, fentanyl and hydrocodone), have contributed significantly to the rise in unintentional poisonings and were listed on the death certificates in nearly 40 percent of all drug poisonings in Ohio in 2008.¹

Research shows that opiate addiction treatment without medication-assisted treatment (MAT) has a relapse rate of 80-95 percent, and behavioral therapy in combination with MAT results in long-term recovery at least 50 percent of the time, similar to other chronic, relapsing diseases like diabetes and hypertension. The Center for Substance Abuse Treatment states that persons who are opiate-addicted have been found to respond best to treatment that combines pharmacological and behavioral interventions.

The proportion of Ohioans accessing services with an opiate abuse/dependence diagnosis has dramatically increased. Nearly 95 percent of treatment providers reported serving clients with opiate abuse/dependence, with slightly more than 58 percent of these providers indicating that the proportion of clients receiving treatment at their agencies for opiate abuse/dependence has increased over the past 12 months. Almost one-third of all providers reported that opiate abusing/dependent clients now make up more than one-quarter of all clients served. Persons seeking treatment for opiate addiction are inundating treatment centers in every region of the state, with the Appalachian region particularly hard hit.

The importance of MAT as an effective evidence-based treatment practice has been increasingly highlighted in recent years. What started with methadone as a treatment modality for opiate addiction was followed by buprenorphine, naltrexone and other alternatives being clinically tried and tested for approval.

With these challenges in mind, during the spring of 2011 ODADAS convened a group of addiction physicians and other clinical experts from around Ohio to develop a clinical protocol for medication-assisted treatment other than methadone. The stated goals were to develop standards of practice for buprenorphine and Suboxone® that would achieve the following:

1. Improve the effectiveness of buprenorphine and Suboxone® therapy
2. Reduce the overall cost of buprenorphine and Suboxone® therapy
3. Decrease the illegal diversion of Suboxone®

¹ Ohio Department of Health. 2010. The Burden of Poisoning in Ohio, 1999-2008. Columbus, OH (October).

The committee met through the summer and early fall of 2011 and recommended the development of a low dose protocol with buprenorphine and Suboxone® to be implemented with individuals with opiate addiction or abuse.

There is a four-phased approach to the buprenorphine and Suboxone® protocol which allows practitioners/physicians to move the patient through the MAT process and monitor appropriately. Throughout each phase, continued treatment with group/individual sessions, attendance at self-help support groups, regular urine analysis and medication compliance checks are essential to the success of this protocol.

The protocol includes:

- Low-Dose Protocol Procedures
- Clinical Assessment Tools
 - Brief Alcohol Monitor (BAM/Addiction Severity Index (ASI))
 - Clinical Opiate Withdrawal Scale (COWS)
 - Checklist
 - Risk Sheet
- Clinical Evaluation Proposal
- Bibliography
- Description of Opiate Treatment Program (OTP)/Federally Qualified Health Center (FQHC) Collaborative in Southern Ohio
- Buprenorphine Maintenance Articles

This *Low Dose Protocol for the Use of Buprenorphine and Suboxone®* contains best practice guidelines recommended for use at Ohio's publicly funded addiction treatment agencies. It is the intention of ODADAS to disseminate this protocol, train practitioners in the use of this protocol, and to make adjustments based on lessons learned from use in Ohio. To the extent possible, ODADAS will have this protocol tested using the NIDA Clinical Trials Network to ensure that this protocol is a best practice for the future of MAT in Ohio.



Medication-Assisted Treatment:

Proposed

LOW DOSE PROTOCOL for the USE of BUPRENORPHINE and SUBOXONE®

Medication-Assisted Treatment Policy Statement

The nationwide epidemic of opiate addiction has devastated Ohio communities as evidenced by the fact that deaths caused by drug overdoses have eclipsed fatalities caused by vehicle crashes for the past three years. Our state has come to the understanding that the opiate epidemic is a healthcare problem and that effective behavioral interventions tied to proven Medication-Assisted Treatment (MAT) like methadone and emerging therapies as in buprenorphine and naltrexone are necessary for sustained recovery and a productive life for the individual.

Research shows that opiate addiction treatment without MAT has a relapse rate of 80-95 percent, and behavioral therapy in combination with MAT results in long-term recovery at least 50 percent of the time, similar to other chronic, relapsing diseases like diabetes and hypertension. The Center for Substance Abuse Treatment states that persons who are opiate-addicted have been found to respond best to treatment that combines pharmacological and behavioral interventions.

According to the National Institute on Drug Abuse (NIDA), "Patients stabilized on adequate, sustained dosages of methadone or buprenorphine can hold jobs, avoid crime and violence, and reduce their exposure to HIV."

GUIDING PRINCIPLES

The following principles will be used to guide the development of medication-assisted protocol in our state:

1. Patients should be fully informed about treatment options (as evidenced by documentation in medical record) including FDA-approved Medication-Assisted Treatments such as methadone, buprenorphine and naltrexone at all levels of care. For programs that do not have MAT available, appropriate referral should be made for patient.
2. Patients receiving opioid agonist or partial agonist therapy should not be treated with opiates for other purposes.
3. Patients receiving opioid agonist or partial agonist therapy should be prohibited from using benzodiazepines or other pharmaceutical products that might put them at the risk for overdose and death.

4. Precautions should be taken to ensure that medications are not diverted for abuse. These precautions should include drug screens, pill counts, and use of a prescription drug monitoring program
5. Prescribing physicians should be encouraged to take continuing medical education regarding the use of Medication-Assisted Treatment and to consult specialists certified by the American Board of Addiction Medicine or certified in Addiction Psychiatry by the American Board of Psychiatry and Neurology.
6. Medication-Assisted Treatment practice standards should change as advanced scientific evidence becomes available, and our state should endeavor to study and refine MAT protocols.
7. Documentation regarding risks of overdose should be present in the clinical record.

Introduction

The pervasiveness of opiate and heroin addiction in Ohio has hit epidemic proportions in recent years. From 1999 to 2008, Ohio's unintentional poisoning death rate increased by 350 percent. Nearly all of those deaths have been due to drug and medication-related poisonings. Opiates, used as pain relievers (such as methadone, oxycodone), have contributed significantly to the rise in unintentional poisonings and were listed on the death certificate in nearly 40 percent of all drug poisonings in Ohio in 2008.¹

An average of four Ohioans die every day from what the Ohio Department of Health refers to as unintentional poisonings. Another significant factor in Ohio's current wave of opiate-related abuse, addiction, and overdose is the growth in prescribing of opiate pain medications. From 1997 through 2010 there was a 900 percent increase in the overall use of opiates in the Ohio healthcare system. This rapid growth in prescribing means more opiate pills sitting in medicine cabinets and more availability for diversion and abuse. The link to unintentional drug overdoses is clear. In fact the statistical correlation between the increase in overdose deaths and prescribed opiate doses reveals a near one-to-one correlation ($r=.979$).²

¹ Ohio Department of Health. 2010. The Burden of Poisoning in Ohio, 1999-2008. Columbus, OH (October).

² Ohio Department of Alcohol and Drug Addiction Services (ODADAS). 2011. Unpublished internal analyses of ARCOS (Automation of Reports and Consolidated Orders System; www.deaddiversion.usdoj.gov/arcos/index.html) rate on grams of opioid distributed and accidental poisoning death rate (Ohio Department of Health). Planning, Outcomes and Research Division.

Quick Facts: Opiate Abuse, Dependence, and Related Overdose Deaths

A quick overview of some of the available relevant statistics on patients seeking treatment for opiate addiction, levels of dispensed opiate medications, treatment outcomes for opiate abusing/dependent clients, and selected other indicators defines the epidemic state of affairs in Ohio.

1. Analysis of admissions for Ohio's current state fiscal year (SFY 2012) shows that patients entering treatment for opiate addiction now account for 28 percent of all persons in treatment.³ Opiate addiction is now the most frequently cited primary drug of choice (except for alcohol) for persons admitted to public addiction treatment centers in Ohio.
2. Overdose deaths with opiates listed on death certificates (heroin, synthetic opioids and psychodysleptics) increased 383 percent from 270 in 2000 to 915 in 2008.⁴
3. In 2010, many Ohio pharmacies dispensed large amounts of opiate medications, with Jackson County in the Appalachian region having the equivalent of more than 130 pills for every man, woman and child residing there.⁵
4. The most current ODADAS Ohio Substance Abuse Monitoring (OSAM) Network report reveals high and increasing availability of opiates across the state, with much of this being attributed to increased prescribing in hospitals, private physicians' offices and pain clinics.⁶
5. Most opiate abusing/dependent clients reported heroin as their drug of choice (43.2 percent), followed by other opiates (37.1 percent) and alcohol and other drugs (19.7 percent).⁷ The vast majority of OSAM Network informants attribute the rise in heroin popularity to prescription opiate users who have switched to heroin use due to the ease and affordability of obtaining heroin over prescription opiates, although prescription opiates remain highly available in all regions.⁸
6. Client treatment admissions for opiate abuse and dependence have risen dramatically over time. Opiate treatment admissions in the Appalachian region tripled from 6.5 percent in 2000 to 19.8 percent in 2010.⁹
7. Opiate abusing/dependent clients have poorer treatment outcomes than any other class of drug abusing/dependent clients. For example, in 2010, only 18.7 percent of clients with heroin or prescription opiates as a drug of choice successfully completed treatment.¹⁰

³ ODADAS. 2010a. Multi Agency Community Information Systems (unpublished internal analysis).

⁴ Ibid, ODH (2010).

⁵ Ohio State Board of Pharmacy (2010; unpublished internal analysis)

⁶ ODADAS. 2011(June). Ohio Substance Abuse Monitoring Network (OSAM): Surveillance of Drug Abuse Trends in the State of Ohio: January-June 2011. Retrieved September 8, 2011, from <http://www.odadas.ohio.gov/public/ContentLinks.aspx?SectionID=5e16593f-93ef-468f-9f8c-1ef8fff0fe29>

⁷ ODADAS. 2010a. Multi Agency Community Information Systems (unpublished internal analysis).

⁸ Ibid, ODADAS (June 2011).

⁹ ODADAS. 2010b. Behavioral Health Module Discharge Data (internal analysis).

8. Currently, Ohio has no formal way of measuring post discharge relapse, but clients do receive a recovery prognosis at end of treatment. Based on this measure, ODADAS estimates that persons admitted to treatment for opiate addiction are almost four times more likely to disengage from treatment early and terminate from care than clients admitted for all other drugs of abuse.

Opiate Addicts and Treatment Outcomes

There is research that examines opiate addiction and treatment outcomes from a variety of approaches. One study affirms the fact that opiate addiction is characterized by high rates of relapse even after long periods of abstinence, requiring new relapse prevention treatments that do not have abuse potential.¹¹ A mid-80s British study that systematically investigated 50 opiate addicts admitted for inpatient treatment found half of them opiate-free when followed up six months after discharge.¹² For United States-based statistics on relapse prevention and treatment failures for opiates, one source notes that relapse rates are 95 percent when treating an opiate addict in a drug-free mode because the brain takes about 35 weeks to return to normal.¹³

Research further indicates that for those who develop addiction, opioid substitution with buprenorphine and medical management of iatrogenic addiction in office settings appears safe and efficacious.¹⁴ The Substance Abuse and Mental Health Services Administration (SAMHSA), in one of its recent treatment intervention protocols, highlighted that similar to patients with other chronic disorders, many who are opiate addicted respond best to treatment that combines pharmacological and behavioral interventions.¹⁵ The study further states that treatment of opiate addiction with maintenance medication and other services for related problems increases the likelihood of ending opiate abuse; and that conversely, ending maintenance medication often results in dropout from other services and a return to previous levels of opiate abuse, with medical and psychosocial consequences.

¹⁰ Ibid, ODADAS (2010b).

¹¹ Tahsili-Fahadan, P., Carr, G. V., Harris, G. C., & Aston-Jones, Gary. 2010. Modafinil Blocks Reinstatement of Extinguished Opiate-Seeking in Rats; Mediation by a Glutamate Mechanism. *Neuropsychopharmacology* 35(11):2203-2210. Published online 2010 July 14. doi: 10.1038/npp.2010.94. PMID: PMC2939923

¹² Gossop, M., Green, L., Phillips, G., & Bradley, B., 1987. "What Happens to Opiate Addicts Immediately after Treatment: a Prospective Follow up Study." *British Medical journal (Clinical Research Edition)* May 30; 294(6584):1377-1380.

¹³ Christensen, Rick. (Undated). Opiate Dependence and Its Treatment. Community Medical Services, Phoenix, AZ; accessed on November 23rd 2011 at http://cmsaz.net/index.php?option=com_content&view=article&id=70:opiate-dependence-and-its-treatment&catid=60:other-articles

¹⁴ Mendelson, J., Flower, K., Pletcher, M. J., & Galloway, G. P. (2008). Addiction to Prescription Opioids. *Experimental and Clinical Psychopharmacology*, 16(5), 435-441. doi:10.1037/a0013637

¹⁵ Center for Substance Abuse Treatment. *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs Inservice Training*. HHS Publication No. (SMA) 09-4341. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2008; reprinted 2009. Accessed on November 23rd 2011 at: http://kap.samhsa.gov/products/trainingcurriculum/pdfs/tip43_curriculum.pdf

In Ohio, the opiate and heroin addiction problem is exacerbated by a historical reluctance among addiction treatment providers to utilize Medication-Assisted Treatment. This abstinence-based philosophy is mentioned in the Ohio statute that governs ODADAS' treatment basis. However, in the past 30 years, a number of promising U.S. Food and Drug Administration (FDA)-approved medications have been tested and used successfully to help people with addictions remain abstinent from their drugs of abuse. ODADAS is now welcoming the use of Medication-Assisted Treatment along with psychosocial therapies to help ensure a drug-free life for citizens with addiction. In this time of scarce resources, client relapse threatens the state's ability to address the opiate threat from a service delivery standpoint. Opiate abuse and related consequences to Ohio communities, families, and the treatment system is an issue of growing significance.¹⁶

An overview of substance abuse treatment service providers in Ohio offers interesting insights. In 2010, the proportion of clients accessing services across Ohio with an opiate abuse/dependence diagnosis dramatically increased. Nearly 95 percent of treatment providers reported serving opiate abusing/dependent clients, with slightly more than 58 percent of these providers indicating that the proportion of clients receiving treatment at their agency for opiate abuse/dependence has increased over the past 12 months. Almost one-third of all providers reported that opiate abusing/dependent clients now make up more than one-quarter of all clients served. Persons seeking treatment for opiate addiction are inundating treatment centers in every region of the state, with the Appalachian region particularly hard hit.

What is even more problematic in Ohio is that while White males are the largest group identified for opiate dependence statewide, providers continue to see an increase in opiate dependence among females, and are now seeing an increase among those in their teens and early 20s. These drugs are most often obtained through prescription, with users reporting ease in feigning pain and of knowing physicians who write prescriptions for payment. In addition, both participants and treatment providers spoke of drug dealers sending people to Florida to purchase opiates to bring back to Ohio. Ohio Substance Abuse Monitoring (OSAM) Network informants consistently highlight that the typical heroin user first abused prescription opiates before progressing to heroin use; thus, Network treatment providers describe prescription opiates as gateway drugs to heroin. According to OSAM data, first-time opiate users are as young as 11-12 years of age and more likely to obtain prescription opiates from medicine cabinets in their home or the homes of relatives or friends.¹⁷

Medication Assisted Treatment: Historical Perspective and Emerging Rationale

Medication-Assisted Treatment is any treatment for opiate addiction that includes a medication (e.g., methadone, buprenorphine,¹⁸ naltrexone) approved by the U.S. Food and Drug

¹⁶ Ibid. ODADAS. 2011 (June). OSAM.

¹⁷ Ibid. ODADAS. 2011 (June). OSAM.

¹⁸ In October 2002, the Food and Drug Administration (FDA) approved buprenorphine monotherapy product, Subutex®, and a buprenorphine/naloxone combination product, Suboxone®, for use in opioid addiction treatment. The combination product is designed to decrease the potential for abuse by injection. Subutex® and Suboxone® are currently the only Schedule III, IV, or V medications to have received FDA approval for this indication. Note that aside

Administration (FDA) for opiate addiction detoxification or maintenance treatment. MAT may be provided in an Opiate Treatment Program (OTP) or an OTP medication unit (e.g., pharmacy, physician's office), or for buprenorphine, a physician's office or other healthcare setting. Comprehensive maintenance, medical maintenance, interim maintenance, detoxification, and medically supervised withdrawal are types of MAT. An OTP can exist in a number of settings, including, but not limited to: intensive outpatient, residential, and hospital settings. Types of treatment include: medical maintenance, medically supervised withdrawal, and detoxification, either with or without various levels of medical, psychosocial, and other types of care.

The FDA approval of the buprenorphine formulations does not affect the status of other medication-assisted opiate addiction treatments, such as methadone and LAAM (levo-alpha-acetyl-methadol).¹⁹ As indicated in Title 42 Code of Federal Regulations Part 8 (42 CFR Part 8), these treatments can only be dispensed in the context of an OTP. Also, neither the approval of Subutex® and Suboxone®, nor the provisions of DATA 2000²⁰, affect the use of other Schedule III, IV, or V medications, such as codeine, that are not approved for the treatment of addiction.

Medication-Assisted Treatment (MAT) is a well-studied and validated pharmacological therapy for the medical condition known as opioid dependence.²¹ National Institute of Health's statement in 1997 advocated that the unnecessary regulations of methadone maintenance therapy and other long-acting opiate agonist treatment programs should be reduced, and coverage for these programs should be a required benefit in public and private insurance programs.²² One study of MAT in an incarcerated population, critiques that although prisons must provide at least the standard of care to prisoners that is available in the general population, Medication-Assisted Treatment, endorsed by international health and drug agencies as an integral part of HIV prevention and care strategies for opiate-dependent drug users, is unavailable to most prisoners.²³

The importance of MAT as an effective evidence-based treatment practice has been increasingly highlighted in recent years. What started with methadone as a treatment modality for opiate addiction was followed by buprenorphine, naltrexone and other alternatives being clinically tried

from Subutex® and Suboxone®, other forms of buprenorphine (e.g., Buprenex®) are not approved for treatment of opioid addiction. Information accessed in November 23, 2011 at: <http://www.buprenorphine.samhsa.gov/about.html>

¹⁹ Ibid, footnote #18.

²⁰ DATA (Drug Addiction Treatment Act of 2000)—refers to **Title XXXV, Section 3502 of the Children's Health Act of 2000**. This act permits physicians who meet certain qualifications to treat opioid addiction with Schedule III, IV, and V narcotic medications that have been specifically approved by the Food and Drug Administration for that indication. Such medications may be prescribed and dispensed by waived physicians in treatment settings other than the traditional Opioid Treatment Program (methadone clinic) setting. Accessed on November 23, 2011 at: <http://buprenorphine.samhsa.gov/data.html>

²¹ Bruce, R. D., & Schleifer, R. A. 2008. Ethical and human rights imperatives to ensure medication-assisted treatment for opioid dependence in prisons and pre-trial detention. *International Journal of Drug Policy*, 19(1), 17-23. doi:10.1016/j.drugpo.2007.11.019

²² National Institutes of Health. Effective Medical Treatment of Opiate Addiction. NIH Consensus Statement Online 1997 Nov 17-19; [cited 2011, November 22nd];15(6):1-38.

²³ Ibid, Bruce and Schleifer (2008).

and tested for approval. In an ongoing search for effective medications for treating opiate addiction, research strongly points not only to improved and effective outcomes for MAT, but also reveals relapse outcomes and treatment failures for treatment approaches without the use of MAT. Arguing that pharmacotherapy is a valuable tool in the clinical armamentarium of addiction treatment, one recent study advocates for strategies to promote adoption of pharmacotherapy for addiction disorders that should be modified to fit the needs of the practice, system, and individual patients. It goes further to state that overcoming barriers to implementation may improve clinical and social outcomes.²⁴

Specifically in the context of treatment resistance with opiate addiction, it has been understood that clients are more likely to relapse and are more at risk for overdose and death than with other drugs of abuse. The promise of MAT's effectiveness is not limited to any one drug, and there are acknowledged problems associated with MAT, such as diversion and use to attain euphoria. However, federally-supported research studies have shown that the most efficacious treatment for opiate dependence are programs that utilize Medication-Assisted Treatment, an evidence-based best practice that couples pharmacotherapies with behavioral therapies.²⁵ The scientific literature examining effective treatments for opiate-dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective treatments for opiate dependence.²⁶

In Ohio's experience, a majority of ODADAS-certified providers reported using one or more evidenced-based program or practice in serving opiate abusing/dependent patients, including Medication-Assisted Treatment. Practically half of referring providers indicated difficulty in getting patients into a physician's office for Suboxone[®]. Cited barriers to clients receiving Suboxone[®] primarily consisted of financial issues (i.e., patient lack of insurance and cost of physician visit and medication), and access issues (i.e., lack of licensed physicians and travel distance to location of licensed physicians).

While most providers know of area physicians licensed to induce/manage Suboxone[®], a majority of providers are not referring to these physicians perhaps due to the high degree of difficulty in patient placement. The majority of providers making methadone referrals also indicated difficulty in placing patients into methadone programs. Cited barriers to patients receiving methadone primarily consisted of capacity issues (i.e., no openings/methadone programs not accepting new patients) and financial issues (i.e., patient lack of insurance and cost of clinic visit and methadone). Given noted capacity issues and widespread difficulty in patient placement, MAT needs to be

²⁴ Oliva, E. M., Maisel, N. C., Gordon, A. J., & Harris, A. H. S. (2011). Barriers to Use of Pharmacotherapy for Addiction Disorders and How to Overcome Them. *Current Psychiatry Reports*, 13(5), 374 - 381. doi:10.1007/s11920-011-0222-2

²⁵ Principles of Drug Addiction Treatment, NIDA, 2009.

²⁶ Minozzi S, Amato L, Davoli M. Maintenance treatments for opiate dependent adolescent. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD007210. DOI: 10.1002/14651858.CD007210.pub2; accessed on November 23, 2011 at <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007210.pub2/abstract>

expanded.²⁷ Regarding the establishment of a Suboxone® Protocol, misuse and abuse of these medications has been widely documented by U.S. and international researchers alike. One such study argues that the level of misuse and abuse of buprenorphine is low relative to the number of prescriptions filled.²⁸

In one study of methadone maintenance treatment that also uses buprenorphine, researchers found that its use could potentially increase treatment completion rates and that those patients who were transferred from methadone to buprenorphine were found to tolerate it well.²⁹ Another study of buprenorphine in a residential therapeutic community also found high success rate.³⁰ An interesting study found MAT to be effective when combined with counseling and education and suggested that buprenorphine be administered on-site and supervised.³¹ Some studies also have looked specifically into at-home administration of buprenorphine for opiate-dependent individuals who originally sought treatment at a hospital. One such study found that at-home administration of buprenorphine was both safe and fiscally sound for approved patients.³²

Policy Implications of Medication-Assisted Therapies

Medication-Assisted Treatment (MAT) is an important component of recovery from opiate addiction. The effectiveness of MAT in opiate treatment has been established, and some states have adopted access to MAT as a quality indicator. Nevertheless, the provision of MAT in the addiction system is low and less than 23 percent of substance abuse treatment facilities in Ohio provide access to any pharmacotherapies.

In recognition of the importance of MAT in the treatment of opiate addiction, Ohio Governor John R. Kasich signed an executive order in February of 2011 authorizing ODADAS and its network of boards and providers to use all FDA-approved medications in the treatment of opiate addiction.³³

²⁷ Ohio Department of Alcohol and Drug Addiction Services [ODADAS]. (November 2010). ODADAS Prescription Drug Opioid Abuse Survey. Retrieved November 23, 2011, from <http://www.odadas.state.oh.us/public/ContentLinks.aspx?SectionID=b6b23cad-6793-4fce-8c8d-2184671edcf7>

²⁸ Smith, M. Y., Bailey, J. E., Woody, G. E., & Kleber, H. D. (2007). Abuse of Buprenorphine in the United States. *Journal of Addictive Diseases*, 26(3), 107-111.

²⁹ Breen, C. L., Harris, S. L., Lintzeris, N., Mattick, R. P., Hawken, L., Bell, J., Ritter, A. J., Lenne, M., & Mendoza, E. (2003). Cessation of methadone maintenance treatment using buprenorphine: Transfer from methadone to buprenorphine and subsequent buprenorphine reductions. *Drug and Alcohol Dependence*, 71, 49-55.

³⁰ Collins, E. D., Horton, T., Reinke, K., Amass, L., & Nunes, E. V. (2007). Using buprenorphine to facilitate entry into residential therapeutic community rehabilitation. *Journal of Substance Abuse Treatment*, 32, 167-175.

³¹ Kresina, T. F., Litwin, A., Marion, I., Lubran, R., & Clark, H. W. (2009). United States government oversight and regulation of medication assisted treatment for the treatment of opioid dependence. *Journal of Drug Policy Analysis*, 2(1), 1-23.

³² Lee, J. D., Grossman, E., DiRocco, D., & Gourevitch, M. N. (2008). Home Buprenorphine/Naloxone induction in primary care. *Journal of General Internal Medicine*, 24(2), 226-232.

³³ Nichols R. (February 2011). Kasich brings new help to prescription drug abuse fight [Internet]. Columbus, OH: Communication Department. Retrieved April 18, 2011, from <http://governor.ohio.gov/LinkClick.aspx?fileticket=xE6jpkQrclY%3d&tabid=70>

Suboxone[®] is the most frequently used therapeutic MAT option in Ohio. The primary ingredient in Suboxone[®] is buprenorphine, a partial opioid agonist with a ceiling effect well below the level that would put patients at risk of respiratory suppression. Buprenorphine also has the unique property of blocking the effect of heroin and other opiate medications. It is therefore widely considered to be a safe and practical alternative to methadone.

Suboxone[®] is also formulated with naloxone, an antagonist that causes immediate opiate withdrawal. The naloxone component of Suboxone[®] is activated only when a patient attempts to use Suboxone[®] in an improper manner.

Currently, many of the DATA 2000 waived physicians in Ohio authorized to prescribe Suboxone[®] for opiate addiction accept cash payment only and require a higher rate of reimbursement for patient visits than is common for other diagnoses. This practice, along with the high cost of Suboxone[®], has rendered this therapy unaffordable for many who could benefit from MAT.

Additionally, practice patterns for the use of Suboxone[®] vary substantially. In some instances physicians and managed care companies allow for only short term use of Suboxone, a practice that NIDA's Clinical Trials Network has proven ineffective and likely to cause relapse. Because of the client's drug-free state immediately post-treatment, relapse for an opiate addict can lead to overdose and death.³⁴

In other instances, patients are dosed above the ceiling effect or at levels that exceed therapeutic requirements. With a street value of approximately \$2 per mg there is great potential for diversion and illegal use.

Establishment of Suboxone[®] Protocol

With these challenges in mind, during the spring of 2011 ODADAS convened a group of addiction physicians and other clinical experts from around Ohio to develop a clinical protocol. The stated goals were to develop standards of practice for Suboxone[®] that would achieve the following:

1. Improve the effectiveness of Suboxone[®] therapy
2. Reduce the overall cost of Suboxone[®] therapy
3. Decrease the illegal diversion of Suboxone[®]

The committee met through the summer and early fall of 2011 and recommended the development of a low dose protocol with buprenorphine and Suboxone[®] to be implemented with individuals with opiate addiction or abuse.

³⁴Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence: A 2-Phase Randomized Controlled Trial. *Archives of General Psychiatry* 2011 (in press)

There are several areas that define the protocol for implementation. Selection Criteria has been established for each physician to review the client's medical and psychosocial history to determine if Suboxone[®] protocol is best suited for their needs. A summary of the session is written and placed into medical chart.

There is a four-phased approach to the Suboxone[®] protocol which allows practitioners/physicians to move the patient through the process and monitor appropriately. Throughout each phase, continued treatment with group/individual sessions, attendance at self-help support groups, regular urine analysis and medication compliance checks are essential to the success of this protocol.

Admission Induction Phase – This phase includes the global and bio-psychosocial assessments which determine the social, occupational and psychological functioning of an individual and how well they approach various daily functions. The Global Assessment of Functioning (GAF) score will be used throughout treatment to determine progress with functional levels. The two instruments that are effective and recommended for the bio-psychosocial in addition to the GAF are the Brief Addiction Monitor (BAM) and the Addiction Severity Index (ASI).

The bio-psychosocial is a clinical tool to determine level of severity of alcohol and drug usage, symptom level/functional outcome and address the seven potential problem areas in substance-abusing patients which include: medical, employment and support, usage, legal status, family/social status and psychiatric status.

The Clinical Opiate Withdrawal Scale (COWS) is also administered upon admission and utilized throughout the induction phase. The COWS is a clinician-administered, pen and paper instrument that rates 11 common opiate withdrawal signs or symptoms. The summed score of the 11 items can be used to assess a patient's level of opiate withdrawal and to make inferences about his or her level of physical dependence on opiates. Scoring and observation determines the level of withdrawal and the degree of medication to be administered. The scoring of the COWS is as follows: 5-12=mild, 13-24=moderate, 25-36=moderately severe and more than 36=severe withdrawal.

A template version of the COWS that can be copied and used clinically is appended (Attachment B). PDF formatted versions of the COWS are also available from the websites of the American Society of Addiction Medicine, the California Society of Addiction Medicine, the UCLA Integrated Substance Abuse Programs, and AlcoholMD.com.\ [PubMed - indexed for MEDLINE]

Induction Phase – This phase is used to determine the appropriate level of Suboxone[®] dosage for each patient. The time between assessment and induction should be within a 24-hour period to capture the “motivational moment.” With the use of the COWS and observation, a patient would be administered 2mg of Suboxone[®] with an observation period. A patient may receive an additional 2mg based upon response, with a maximum dose of 4mg on Day One. This process could continue over a four-day period with an overall max of 16mg of Suboxone[®] for stabilization.

- **Patients not currently tolerant to opioids** – Currently non-opioid tolerant individuals with a history of opiate dependence who are at high risk for relapse because of recent release from a controlled environment and who wish to receive treatment, should be started at no more than 2mg daily. The dose should be increased slowly (by increments of no more than 2mg every 5-7 days. This may vary, depending on the amount of time since the last use of an opioid.
- **Patients using Suboxone® illicitly at the time of presentation to the clinic** – These patients may not be in withdrawal as they are using Suboxone® to help manage their withdrawal on their own. The physician should assess the amount and frequency with which the patient is using illicit Suboxone®. Many patients using Suboxone® in this way are only using whole tablets and have not tried intermediate doses of Suboxone® such as 12mg. A rapid buprenorphine test should be performed to assess for the presence of buprenorphine in the urine. For these individuals, it is generally recommended to start at 8-12mg of Suboxone® on the first day.
- **Patients transferring from Methadone Maintenance** – Buprenorphine may precipitate withdrawal in patients transferring from methadone. This is most likely to occur in patients on higher doses of methadone. In coordination with the methadone program, the methadone dose should be gradually tapered to 30mg per day and maintained at this dose (or lower) for 5-7 days. The patient should then abstain from any methadone for 48-72 hours prior to initiating buprenorphine. He/she should have clear objective signs of opiate withdrawal prior to receiving buprenorphine.

Stabilization Phase – This phase is usually a period of 18-24 months, based upon the patient’s response to Suboxone® on a daily basis. The first four to six weeks of this phase can be used by physicians to “step down” patients who may have initially received 16mg either 12mg or 8mg depending on their symptoms. This phase also includes regular involvement of a treatment regime to include individual/group counseling minimum weekly, regular attendance of self-help groups as established by the individualized treatment plans and regular urinalysis and medication compliance checks. Counseling methods should be evidence based and may include behavioral techniques, cognitive-behavioral therapy, contingency management, or other counseling approach with documented efficacy with this population. This may also include cross-theoretical evidence-based approaches including 12-Step Facilitation. It is expected the patient will participate in counseling, self-help group activity, urinalysis, and medication compliance checks throughout this phase of treatment. Documentation of appropriate linkage to medical home, family doctor, Primary Care Physician (PCP), Federally Qualified Health Center (FQHC) should be noted in medical record.

Tapering Phase – This phase is used for the purpose of reduction of medication. Each patient will begin a reduction of 25-50 percent every two weeks until 1mg is achieved. This level of 1mg should be maintained for approximately 2-3 weeks then discontinued. The tapering phase may vary with individuals based upon response to medication and reduction. Continued treatment and self-help groups are imperative along with urinalysis and medication compliance checks.

LOW DOSE PROTOCOL for the USE of BUPRENORPHINE and SUBOXONE®

- I. **Selection Criteria include checklists to determine eligibility. (See Attachment E)**
- II. **Summary by physician on eligibility for each patient**
- III. **Admission Induction Phase to include:**
 - a. **Global Assessment of Functioning (GAF)** - subjectively rate the social, occupational, and psychological functioning of adults, e.g., how well or adaptively one is meeting various problems-in-living.
 - b. **Brief Addiction Monitor (BAM)/Addiction Severity Index (ASI) –**

BAM- The Brief Addiction Monitor (BAM) is a 17-item, multidimensional questionnaire designed to include both symptom level outcomes as well as functional outcomes.

ASI- The Addiction Severity Index (ASI) is a semi-structured interview designed to address seven potential problem areas in substance-abusing patients: medical status, employment and support, drug use, alcohol use, legal status, family/social status and psychiatric status.
 - c. **Clinical Opiate Withdrawal Scale (COWS)** - The Clinical Opiate Withdrawal Scale (COWS) is an 11-item clinician-administered scale assessing opiate withdrawal.
- IV. **Induction Phase - Administer first dosage with observation for presence of side effects –** Using COWS scale, administer 2mg of Suboxone® with observation and continue up to 4mg daily max to begin stabilization. This process could continue over a 4-day period with an overall max of 16mg.

Stabilization Phase – This phase is usually a period of 18-24 months, based upon the patient's response to Suboxone® on a daily basis. This phase also includes regular involvement of a treatment regime to include individual/group counseling weekly, regular attendance of self-help groups and regular urinalysis and medication compliance checks. Counseling methods should be evidence-based and may include behavioral techniques, cognitive-behavioral therapy, contingency management, or other counseling approach with documented efficacy with this population. This may also include cross-theoretical evidence-based approaches including 12-Step Facilitation. It is expected the patient will participate in counseling, self-help group activity, urinalysis, and medication compliance checks throughout this phase of treatment. Documentation of appropriate linkage to medical home, family doctor, Primary Care Physician (PCP), Federally Qualified Health Center (FQHC) should be noted in medical record.

- V. Tapering Phase** – The reduction of medication by 25-50 percent every two weeks until 1mg is achieved. Maintain for 2-3 weeks then discontinue. Tapering phase may vary with individuals.

ODADAS consulting physician Dr. Phillip Prior is currently using this method to determine dosing at induction and is maintaining patients on 8mg instead of the more common 16mg. Dr. Ted Parran, practicing addictionologist with the Case Western Reserve University School of Medicine and Medical Director for Rosary Hall at St. Vincent Charity Hospital, is also dosing at this level. Neither physician has noted any decline in treatment efficacy at the lower dose. Dr. Parran has published results supporting the recommended lower dosing practice. (“Urban Office-Based Buprenorphine/Naloxone Opioid Maintenance Therapy: Outcomes at 18 Month Follow-Up” Adelman and Parran et al. August 2009)

A recent large multi-site randomized clinical trial found that of 653 patients, 8.1 percent were able to maintain “mild” opiate withdrawal symptoms (defined as a score < 12 on the COWS) when given 8mg of buprenorphine/naloxone per day, while 17.8 percent were able to do this on 12 mg, and 38.3 percent were able to do this when given 16mg per day. This emphasizes the need for close monitoring and individualization of treatment based on the patient’s dose response (Weiss et al. 2011).³⁵

VI. Provide medication to patients for longer periods of time

Emerging evidence suggests that Medication-Assisted Treatment may be required for longer periods of time. Clinical evaluation protocol will be established to determine relapse rates for varying periods of MAT. This may require up to 18 months or longer. MAT protocol should be flexible enough to meet the needs of each patient in his or her own recovery process.

Reports over the past 30 years from methadone maintenance treatment studies (the other Opiate Maintenance Treatment [OMT]) indicate that persons stable and doing well on methadone for greater than 18-24 months tend to have better outcomes when they taper off of methadone than those who have done well but have been on OMT less than 18 months when they attempt to taper off. In addition, there is data about stability of sobriety from a totally different perspective, namely the 75 years of empirical experience of the Alcoholics Anonymous (AA) program. Twelve-step programs have traditionally required two years of uninterrupted sobriety before encouraging recovering persons to consider serving as a

³⁵ Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MN, Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, **Somoza EC**, Sonne SC, Ling W. Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence: A 2-Phase Randomized Controlled Trial. Arch Gen Psychiatry. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MN, Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, Ling W. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence a 2-phase randomized controlled trial. Arch Gen Psychiatry 2011;68:1238-1246.

sponsor for others. Therefore, based upon the data from these very different perspectives on stability of recovery, it is recommended that patients treated with buprenorphine maintenance as an adjunct to their sobriety program be urged to continue on OMT for at least 18 months before tapering off OMT.

VII. Use rigorous protocol for tapering patients from higher to lower doses and from lower doses to no medication.

Any patient whose dosage level is higher than 16mg will be reduced to 16mg. The opiate receptors are saturated at this level. A 25-50 percent reduction in dosage, with observation, will occur each appointment until 25 percent is no longer practical.

Buprenorphine is an exceptionally potent opioid, with milligram-for-milligram research indicating that it is 20-50 times more potent than morphine (v.o. Rollie “Ed” Johnson MD, Medical Director for Reckitt-Benckiser and former career senior researcher at the Opioid Research Branch of the NIDA). As such, it has been underestimated in potency both from the perspective of often using higher doses than necessary in OMT and intending to taper patients much too quickly from the drug when OMT is being concluded as an aspect of a patient’s recovery program.

- a. Doses of buprenorphine above 16mg/d should be uniformly discouraged for all patients, whether in the publicly-funded or privately-funded addiction treatment infrastructure. Publicly-funded treatment involving buprenorphine experiences the medication as the most expensive aspect of the treatment program after the initial phase of IOP/OP and aftercare/continuing care is completed. There is no published data indicating a clear therapeutic advantage of higher range (12-16mg/d) buprenorphine compared to lower dose range (8-12mg/d). There is one pending report (Parran et. al., 2011) indicating that the lower dose range (8mg/d when compared with 16mg/d), while leaving patients less comfortable, appears to have resulted in the same rates of abstinence and treatment retention.³⁶ In order to provide treatment through the publicly-funded infrastructure to as many patients as possible, use of the 8mg/d dose is recommended.
- b. When tapering a patient off of a given dose of buprenorphine, there are again few published reports to help guide management. It is clear that many patients who are tapered off have a high risk for relapse. It is also clear that buprenorphine has a long half-life perhaps longer than two days. Any time a dose of ANY medication is changed it requires approximately five lives to achieve a new “steady state” blood level. With psychoactive medications it requires perhaps three “steady states” to

³⁶ Parran TV, M.D., et al Buprenorphine/naloxone Maintenance Therapy: the Effect of Dose on Two Year Retention in an Office-based Treatment Program, 2011.

develop tolerance to this new blood level. Therefore, for buprenorphine, dose decreases in the lower end of the taper (perhaps the last third of the original maintenance dose) probably should be made no more frequently than once every two to four weeks. For practical purposes, a tapering strategy engineered for minimal patient discomfort/withdrawal symptoms/cravings could be as follows:

- i. FIRST THIRD OF THE MAINTENANCE DOSE – taper down over 6-8 weeks with divided dose cuts every two weeks.
- ii. MIDDLE THIRD OF THE MAINTENANCE DOSE – taper down over 6-12 weeks with divided dose cuts every three weeks.
- iii. LAST THIRD OF THE MAINTENANCE DOSE – taper over three to six months with divided dose cuts every three to four weeks.

VIII. Establish a clinical evaluation process to determine the effectiveness of the new protocol and make adjustments over time to assure the addiction system is using the best science possible to treat opiate addicted Ohioans. (SEE ATTACHMENT G)

IX. Resource documents:

1. Low-Dose Protocol Procedures
2. Clinical Evaluation Tools
 - a. BAM/ASI
 - b. COWS
 - c. Checklist
 - d. Risk Sheet
3. Clinical Evaluation Proposal
4. Formal Bibliography
5. Description of Southern Ohio OTP
6. Proposal for Federal Funds
7. Dr. Parran – Buprenorphine Maintenance Articles
(Please see attachments)

Summary of Proposed Project in Jackson County

Background

Ohio's Appalachian counties are faced with an unprecedented opiate abuse epidemic. Data from the Ohio Department of Health (ODH) suggests that from 2000 to 2008, the state experienced a 300 percent increase in opiate-related deaths. Findings from the Ohio State Board of Pharmacy show that the 2010 per capita dose rates of opiates ranged from 18.2 in Holmes County to 130.2 in Jackson County, with a statewide average of 67 pills per person (up from 7 pills per person in 1997.) The ODH Office of Vital Health Statistics reports that the majority of unintentional drug overdoses from 2001 (slightly under 600) through 2007 (nearly 1,400) were the result of prescription drugs. Opiates have become the most frequently reported drug of choice in Ohio's Appalachian Counties.

According to CareSource, a Medicaid managed care organization (MCO) serving the Appalachian region, the total average 2010 medical costs per member per month (PMPM) were seven times higher for chronic opiate users (\$1,370 PMPM) compared with non-users (\$191 PMPM). Further, chronic opiate users represent only 10 percent of the MCO's enrollee population.

Regional Opiate Treatment Program

One solution to reducing opiate abuse and dependence is the establishment of an opiate treatment program (OTP) accessible to residents of Ohio's Appalachian counties and located in Jackson County, the area most severely affected by opiate abuse. Currently, all 12 of Ohio's OTPs are located in urban centers. A traditional OTP often operates as a stand-alone program and is required to meet state and federal certification requirements. While OTPs focus mainly on addressing addiction through a medication intervention, they also offer counseling sessions in both an individual and group format. OTPs have not traditionally offered co-occurring treatment (mental health and substance abuse) nor have they focused on the provision of primary care. Of all the treatment regimens, OTPs have tended to provide a well-regulated and specialized type of service.

ODADAS and its partners are planning the creation of an OTP in Jackson County that serves as a multi-disciplinary, integrated healthcare organization that provides evidence-based medicine for the treatment of chemical dependency, mental illness and other medical conditions that often co-occur with substance abuse (e.g., hepatitis, HIV/AIDs, tuberculosis, kidney disease, hypertension, diabetes). The OTP would be structured to provide care through a whole-person approach and for this reason, would operate as part of a Community Health Center (CHC), also referred to as a federally qualified health center or FQHC.

The goal of the FQHC program is to maintain, expand and improve the availability and accessibility of essential primary and preventive health care services (and related enabling services such as case management, patient education and outreach) for low-income, medically underserved and vulnerable populations that have traditionally had limited access to affordable services and face the greatest barriers to accessing care. FQHCs must be located in and/or serve areas in the greatest need; must serve the full "life cycle" of care (prenatal, pediatrics, adolescent, adult, geriatric)

through a core staff of primary care providers; and must be governed by a community board with a majority of members who are users of the health center.

Over time we expect the OTP-FQHC Collaborative to result in lower rates of opiate abuse and addiction among Ohio's Appalachian residents, fewer emergency department visits for primary care and behavioral health issues, fewer arrests and use of local jails and court systems and fewer children entering into foster care.

OTP-FQHC Collaborative Services and Clinical Approach

In order to address health needs of individuals with opiate addiction age 18 and older and ensure access to other services that affect recovery and improve health outcomes, the OTP-FQHC Collaborative would be structured to provide:

- Medication-Assisted Treatment for opiate addiction at the OTP-FQHC Collaborative site
- Primary Care at the OTP-FQHC Collaborative site
- Screening and Brief Intervention at the OTP-FQHC Collaborative site
- Hospital Emergency Department (ED) diversion
- Comprehensive care management services at the OTP site
- Substance Abuse and Mental Health Treatment by Existing Local Behavioral Health Providers

Benefits of the Proposed Model

It is anticipated that the proposed structure, collaborative partnerships and clinical approach will not only yield improved health outcomes for Ohio's Appalachian community with opiate addiction, but also will allow the state to test new and existing opportunities to provide sustainable and cost-effective services. To illustrate:

1. Establishing the OTP as part of a Community Health Center enables the center to utilize 340(b) drug pricing. The federal 340(b) program allows CHCs to purchase covered outpatient prescription pharmaceuticals for patients at substantially discounted prices.
2. Integrating the OTP into an FQHC provides care through a whole-person approach and allows for the management of individuals with chronic conditions in addition to their opiate addiction.
3. Locating a regional OTP in Jackson County provides accessible services to residents in nearby counties (e.g., Athens, Gallia, Lawrence, Pike, Ross, Scioto and Vinton) where the impact of opiate abuse and addiction has been equally devastating on communities and families.

Attachment A

MAT PROTOCOLS FOR SUBOXONE®

I. Selection Criteria: Please refer to checklist

- A. Checklist to be reviewed with patient
- B. Signed off by Physician

1. Written Eligibility Summary: Please refer to summary

- A. Summary to be written for each patient
- B. Signed off by Physician

II. Admission Induction Phase

A. Administer the Global Assessment Functioning (GAF)

May be administered by the following:

Physician

Licensed Professionals as stated in OAC – 3793:2-1-08 Treatment Services

B. Administer the Addiction Severity Index (ASI) or Brief Addiction Monitor (BAM)

May be administered by the following:

Physician

Licensed Professionals as stated in OAC – 3793:2-1-08 Treatment Services

C. Administer the Clinical Opiate Withdrawal Scale (COWS)

Physician

Licensed Professionals as stated in OAC – 3793:2-1-08 Treatment Services

D. Administer first dosage with Observation (approx. 2 hours) for presence of side effects

- 1. Results of COWS <11 – First dose 2mg of suboxone
- 2. Results of COWS ≥ 11 - First dose 4mg of suboxone
- 3. If continued withdrawal symptoms are observed with COWS ≥ 8 two hours after initial dose, initial dose is repeated. Max dosage for Day 1 = 8mg of Suboxone®.

After 4 hours observation patient is sent home with clear instructions that they have narcotic blockade in effect and cannot use narcotics.

4. Day 2 – if withdrawal is still evident (COWS \geq 8) initial dose is provided along with an additional 4mg, with observation. Max dosage is 12mg.
5. Day 3 – if withdrawal is still evident (COWS \geq 8) Day 2 dose is provided along with an additional 4mg, with observation. Max dosage is 16mg.
6. Day 4 forward – maintenance on Day 3 dose.

III. Stabilization Period

- A. Usually a period of 18-24 months of maintaining dosage established.
- B. Dosage continued on daily basis.
- C. Counseling methods should be evidence-based and may include behavioral techniques, cognitive-behavioral therapy, contingency management, or other counseling approach with documented efficacy with this population. This may also include cross-theoretical evidence based approaches including 12-Step Facilitation.
- D. It is expected the patient will participate in counseling, to include individual/group counseling minimum weekly, regular attendance of self-help groups as established by the individualized treatment plans, urinalysis, and medication compliance checks throughout this phase of treatment.
- E. Regular urinalysis according to OAC 2-1-08. For the purposes of the protocol, “regular” will be understood to mean weekly.
- F. Medication compliance- pill counts.

IV. Tapering Stage

- A. Reduction of medication by 25-50 percent every 2 weeks until 1mg is achieved.

Attachment B

CLINICAL OPIATE WITHDRAWAL SCALE (COWS)

For each item, circle the number that best describes the patient’s signs or symptom. Rate on just the apparent relationship to opiate withdrawal. Have the patient sit in a quiet, relatively stimulus-free room for 5-10 minutes prior to administering the scale.

Client’s Name: _____		Date of Birth: _____
Date: _____		Time: _____
<p>Resting Pulse Rate: _____ beats/minute <i>Measured after patient is sitting or lying for 2-3 minutes</i> 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120</p>	<p>GI Upset: <i>Over past ½ hour</i> 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting</p>	
<p>Sweating: <i>Over past ½ hour; not accounted for by room temperature or patient activity.</i> 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face</p>	<p>Tremor <i>Observation of outstretched hands</i> 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching</p>	
<p>Restlessness <i>Observation during assessment</i> 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds</p>	<p>Yawning <i>Observation during assessment</i> 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute</p>	
<p>Pupil size <i>Observation during assessment</i> 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible</p>	<p>Anxiety or Irritability Self report & Observation during assessment 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult</p>	
<p>Bone or Joint aches <i>If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored</i> 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort</p>	<p>Gooseflesh skin <i>Observation during assessment</i> 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection</p>	
<p>Runny nose or tearing <i>Not accounted for by cold symptoms or allergies</i> 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks</p>	<p>Total Score _____ (The total score is the sum of all 11 items)</p> <p>Initials of person completing Assessment: _____</p>	

Withdrawal score severity: 5-12 = mild 13-24 = moderate 25-36 = moderately severe >36 = severe

Attachment C

BRIEF ADDICTION MONITOR

Instructions:

*This is a standard set of questions about several areas of your life such as your health, alcohol and drug use, etc. The questions generally ask about the **past 30 days**.*

Please consider each question and answer as accurately as possible.

Method of Administration:

Clinician Interview Self Report Phone

1. In the past 30 days, would you say your physical health has been?

0-Excellent 1-Very Good 2-Good 3-Fair 4-Poor

2. In the past 30 days, how many nights did you have trouble falling asleep or staying asleep?

3. In the past 30 days, how many days have you felt depressed, anxious, angry or very upset throughout most of the day?

4. In the past 30 days, how many days did you drink ANY alcohol?

___ ___ (If 00, *Skip* to #6)

5. In the past 30 days, how many days did you have at least 5 drinks (if you are a man) or at least 4 drinks (if you are a woman)? [One drink is considered one shot of hard liquor (1.5 oz.) or 12-ounce can/bottle of beer or 5-ounce glass of wine.]

6. In the past 30 days, how many days did you use any illegal/street drugs or abuse any prescription medications?

___ ___ (If 00, *Skip* to #8)

7. What did you take? (*Check* all that apply)

7A. Marijuana (cannabis, pot, weed)?

7B. Sedatives/Tranquilizers (e.g., "benzos", Valium, Xanax, Ativan, Ambien, "barbs", Phenobarbital, downers, etc.)?

7C. Cocaine/Crack?

7D. Other Stimulants (e.g., amphetamine, methamphetamine, Dexedrine, Ritalin, Adderall, "speed", "crystal meth", "ice", etc.)?

7E. Opiates (e.g., Heroin, Morphine, Dilaudid, Demerol, Oxycontin, oxy, codeine (Tylenol 2,3,4), Percocet, Vicodin, Fentanyl, etc.)?

7F. Inhalants (glues/adhesives, nail polish remover, paint thinner, etc.)?

7G. Other drugs (steroids, non-prescription sleep/diet pills, Benadryl, Ephedra, other over-the-counter/unknown medications)?

8. In the past 30 days, how much were you bothered by cravings or urges to drink alcohol or use drugs?

0-Not at all 1-Slightly 2-Moderately 3-Considerably 4-Extremely

9. How confident are you in your ability to be completely abstinent (clean) from alcohol and drugs in the next 30 days?

0-Not at all 1-Slightly 2-Moderately 3-Considerably 4-Extremely

10. In the past 30 days, how many days did you attend self-help meetings like AA or NA to support your recovery?

11. In the past 30 days, how many days were you in any situations or with any people that might put you at an increased risk for using alcohol or drugs (i.e., around risky “people, places or things”)?

12. Does your religion or spirituality help support your recovery?

0-Not at all 1-Slightly 2-Moderately 3-Considerably 4-Extremely

13. In the past 30 days, how many days did you spend much of the time at work, school, or doing volunteer work?

14. Do you have enough income (from legal sources) to pay for necessities such as housing, transportation, food and clothing for yourself and your dependents?

0-No 4-Yes

15. In the past 30 days, how much have you been bothered by arguments or problems getting along with any family members or friends?

0-Not at all 1-Slightly 2-Moderately 3-Considerably 4-Extremely

16. In the past 30 days, how many days were you in contact or spent time with any family members or friends who are supportive of your recovery?

17. How satisfied are you with your progress toward achieving your recovery goals?

0-Not at all 1-Slightly 2-Moderately 3-Considerably 4-Extremel

Time Finished: _____:_____

Attachment D

ADDICTION SEVERITY INDEX

(Full ASI is available at this link.)

http://www.tresearch.org/resources/instruments/ASI_5th_Ed.pdf

Attachment E

SELECTION CRITERIA CHECKLIST

- (1) Patient abstinent from opiates for 24 hours
(96 hours if on methadone) or exhibiting WD Sx Yes
- (2) Liver enzymes normal in past 2 months
(order STAT if not) Yes
- (3) Hepatitis profile
(or clinical Hx) Yes
 Neg
 Pos
- (4) Pregnancy test in last week Neg
 Pos
 N/A
- (5) Patient off all benzodiazepines Yes
- (6) Suboxone[®] info. sheets reviewed by client Yes
- (8) Consents signed:
 Buprenorphine Tx Yes
 ADD contract Yes
 Opioid agreement Yes
 OARRS check Yes
- (9) Physician intake note Yes
- (10) Dosing instructions provided Yes
- (11) Rx at pharmacy Yes
 N/A (inpatient)
- (12) Pre-induction note (labs drawn, consents signed) Yes
- (13) Clinical data base (general past medical history) Yes
- (14) Does the patient have a diagnosis of opioid dependence? Yes
- (15) Does the patient understand the risks and benefits of
 Buprenorphine treatment? Yes

- (16) Is the patient psychiatrically stable? _____ Yes
- (17) Is the patient actively suicidal or homicidal; has he or she recently attempted suicide or homicide? _____ No
- (18) Does the patient exhibit emotional, behavioral, or cognitive conditions that complicates treatment? _____ No
- (19) Is the patient currently dependent on or abusing alcohol? _____ No
- (20) Does the patient have a history of multiple previous treatments or relapses, or is the patient at high risk for relapse to opioid use? _____ No
- (22) Is the patient using other drugs? _____ No
- (23) Has the patient had prior adverse reactions to buprenorphine? _____ No
- (24) Does the patient have medical problems that are contraindications to buprenorphine treatment? _____ No
- (25) Are there physical illnesses that complicate treatment? _____ No

Attachment F

RISK INFORMATION SHEET:

Risk factors for relapse into opiate dependency:

- No alternative for housing currently other than returning to a high-risk environment.
- Failed previous attempts at recovery without ORT.
- History of high-dose narcotic use with probable subsequent receptor dysregulation.
- Continued intense opiate cravings despite an adequate conventional recovery program.
- Recent transient relapse.

Additional factors favoring use of ORT include:

- History of previous success with ORT.
- History of high-risk behavior surrounding opiate use.
- Ability to minimize potential for diversion.

Factors arguing against use of Suboxone® include:

- Refusal to actively participate in a conventional recovery program.
- Pain management issues.
- History of relapse on ORT.
- Transition from methadone.
- Oral issues precluding use of a sublingual med.
- Seizure disorder.
- History of benzodiazepine misuse.
- Inability to arrange reliable follow-up.
- Dementia or other cognitive dysfunction.
- Refusal to enter withdrawal prior to induction.
- Use of tramadol.
- Poly-substance dependency.

Attachment G

Ohio's Proposed Opiate Treatment Program FQHC Collaborative

Program Evaluation

The Program Evaluation will be conducted by the Cincinnati Addiction Research Center (CinARC) located within the Department of Psychiatry and Behavioral Neuroscience at the University of Cincinnati College of Medicine. CinARC is home to the Ohio Valley Node (OVN) of the National Institute on Drug Abuse's (NIDA) Clinical Trials Network (CTN). The CinARC team has more than 16 years of experience conducting research on state-of-the-art treatment for substance use disorders, as well as extensive experience with Medication-Assisted Treatment for opiate dependence.

Methods. Overall the goal of the program evaluation is to determine the population- and patient-level outcomes associated with opiate treatment at the FQHC, as well as provide a preliminary assessment of cost-effectiveness. A mixed-method approach will be utilized to achieve this goal. Observational methods will be used to collect population-level outcomes (e.g., rate of access to drug treatment, drug overdose rate, number of drug-related arrests) within Jackson County for one-year prior to the opening of the FQHC and one-year after the FQHC was opened. Patient-level outcomes will be collected by prospectively interviewing and following 75 opiate-dependent patients who are treated at the FQHC over a period of six months.

Procedures. The program evaluation will be conducted over a period of 18 months and is scheduled to begin once the FQHC opens. The first three months of the study, while the FQHC is fine-tuning clinical operations, will be used to 1) collect the observational data, 2) develop the database for the prospective study in RedCAP (a web-based database and online survey tool), and 3) submit for IRB approval. Publically available data from the Ohio Department of Health and criminal justice departments in Jackson County will be extracted and entered into a Stata database by a Research Assistant (RA) at CinARC.

The second phase of the study will be a six-month period during which FQHC patients with a primary diagnosis of opiate dependence that meet the study inclusion/exclusion criteria will be prospectively enrolled until a sample size of 75 subjects is achieved. The baseline assessment will take less than two hours and the follow-up assessment will take less than one hour. At three- and six-months post baseline enrollment, follow-up interviews will be conducted over the telephone (and/or via the internet if possible). Subjects will receive a reimbursement, gift card for local goods/services, of \$25 for each follow-up assessment that is completed. All study data will be entered into a RedCAP database and procedures will be implemented to ensure the quality and security of the data. The RedCAP software meets the federal guidelines regarding the protection of patient health information. A Research Assistant will be located at the FQHC to enroll, interview and track study participants.

The third phase of the study will include a six-month period to finalize all follow-up assessments with study participants and a three-month period to collect the second-wave of observational data,

as well as conduct data analysis and write a final report. If possible, cost data from the FQHC's electronic health record will be extracted to determine the total costs of providing treatment for study participants. The Program Evaluation Director, Dr. Erin L. Winstanley, will supervise all study staff and will conduct the statistical analysis.

Participants. The study would consecutively enroll patients (n=75) that present at the FQHC during a six-month study enrollment period and meet the study inclusion/exclusion criteria for the study. The inclusion criteria are 1) 18 years of age or older, 2) primary diagnosis of opiate dependence, and 3) willing/able to provide consent. The exclusion criteria are: 1) living greater than 45 miles from the FQHC, 2) unable to provide collateral contact information, and 3) non-English speaking. The program evaluation will focus on patients for whom the FQHC will be their medical home and will exclude patients whose treatment utilization may be curtailed by geographic distance or the cost of transportation.

Measures. The primary outcome measures are: 1) self-reported days of opiate use and 2) number of days worked. The secondary outcome measures are: 1) drug treatment utilization (e.g., retention in treatment, utilization of MAT, modalities of services), 2) medical care utilization (e.g., number of visits to the emergency room, receipt of preventative services), 3) number of days under criminal justice supervision (e.g., including jail, prison, probation, or parole) and 4) involvement with the Office of Families and Children. The Addiction Severity Index (ASI) Lite will be used to collect information on the patient's psychiatric, medical, employment, legal and family/social problems. The 12-item Short-Form Health Survey (SF-12) will be used to assess the patient's medical status. The study instruments will be administered by the Research Assistant at baseline, 3-months post admission and 6-months post admission to the FQHC. Finally, the follow-up assessment at three-months will include a patient-reported survey of satisfaction with treatment services received at the FQHC.

Analysis. The statistical analysis will be conducted in Stata SE 11.2 and SAS 9.2. Descriptive statistics will be used to summarize the sociodemographic/clinical characteristics of the study participants and the results of the patient satisfaction survey. The observational data will be analyzed by comparing the proportion of the Jackson County population that experiences the consequences of opiate dependence pre- and post- implementation of the FQHC. The prospective study results will be analyzed using a longitudinal regression model (GEE) to determine whether the study participants' treatment outcomes improved over time. The GEE statistical model will include a term for time, severity of addiction, previous drug treatment exposure, and involvement with the criminal justice system. A sensitivity analysis will be conducted to determine the robustness of the GEE model and will include subscale scores from the ASI, as well as the SF-12 total score. If cost data is available electronically, the results will be summarized and broken down by treatment modality.

All of the program evaluation results will be synthesized in a report and it is anticipated that the results of this study will be used as pilot data for a future grant submission to NIDA. The next steps would be to develop a randomized clinical trial to determine the outcomes of integrated drug and medical treatment at the FQHC compared to "treatment as usual" in southeast Ohio.

Attachment H

Buprenorphine/naloxone maintenance therapy: the effect of dose on two-year retention in an office-based treatment program

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Dr. Parran had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ABSTRACT

Context

Buprenorphine has been available for office-based opioid maintenance in the treatment of narcotic addiction for the past seven years, but few reports indicate the dose range necessary to adequately maintain patients. We report on the effect of 8 mg/d v. 16 mg/d of buprenorphine on long term patient retention in office based opioid maintenance treatment (OBOMT).

Objective

To evaluate the effect of the daily maintenance dose of buprenorphine between 16 mg/d to 8 mg/d on two year patient retention in an office based opioid maintenance treatment program.

Design, Setting, and Participants

Cohort controlled retrospective chart review of urban hospital based primary care clinic treating 158 opiate dependent, low socio-economic status, un-insured, non-homeless patients in a grant funded comprehensive treatment program including up to two years of buprenorphine pharmacotherapy.

Intervention

The comprehensive treatment program consisted of residential treatment, intensive out-patient and aftercare counseling, and OBOMT. Due to State funding cuts, after two years the program decreased the buprenorphine maintenance dose from 16mg/d to 8mg/d for all subsequent admissions. We report on patient retention during the two years of 16mg/d dose therapy (cohort 1) and two years of 8mg/d dose therapy (cohort 2).

Main Outcome Measures

The primary outcomes of this study, formulated prior to the retrospective chart review, were to measure and compare patient retention in the two cohorts at each point of treatment transition: inpatient induction, residential treatment, intensive outpatient counseling, aftercare monitoring, and one year in buprenorphine clinic.

Results

Surprisingly, there were no differences in patient retention at the end of each level of care between the 16mg/d cohort and the 8mg/d cohort. Overall, 48 % of patients who started on OBOMT were still enrolled after over 1 year, with no difference in retention rate between the two cohorts.

Conclusions

Lower dose buprenorphine maintenance (8mg v. 16mg) in uninsured patients enrolled in a publicly funded long-term OBOMT was as effective as higher dose therapy in promoting patient retention throughout a two year study period. This lower dose resulted in a substantial saving to the public funding agency. This data has implications for public and managed care funding of OBOMT, and for the general prescribing of buprenorphine in out-patient care and may also be useful in the ongoing debate about the relationship between buprenorphine dose and the risk of buprenorphine diversion.

Keywords: buprenorphine, office-based, dose, retention, treatment cost, diversion
Word count: 1922

INTRODUCTION

Approved by the FDA in October of 2002, the buprenorphine/naloxone sublingual combination tablet (Suboxone®) (hereafter referred to as bup/nx) became available for use in office-based opioid maintenance therapy (OBOMT) for opioid dependent patients and became the first opioid agonist approved for use in this setting¹. This paved the way for major changes in the way opioid addiction is treated in the United States, potentially making opioid maintenance therapy available to a much larger population of patients¹⁻⁴. Despite significant oversight and monitoring of buprenorphine maintenance in the United States, the seven years since FDA approval have left many clinical issues unresolved. This report addresses questions surrounding the effect of bup/nx dose on treatment retention and the indirect implications dosing practices have on growing concern regarding bup/nx diversion.

Many issues regarding office-based buprenorphine maintenance have been well studied. These include data about the pharmacology of buprenorphine⁵⁻⁷, the effect of different dosing intervals on patient retention,⁸⁻¹⁰ and comparisons of efficacy versus methadone in opioid maintenance treatment.¹¹⁻²⁵ Understanding has evolved regarding the optimal dose ranges of buprenorphine including a therapeutic effect in the 8-16mg range, a ceiling effect in the 24-32mg range,⁶ and efficacy in improving treatment retention and increasing abstinence over a range of dosing intervals including daily and thrice weekly schedules.^{10,25}

Some of the questions that remain regarding buprenorphine include exploring potential utility in chronic pain and addiction populations, intermediate and short term use for stabilization and medical withdrawal, and the effect of dose on retention when used in office-based opioid maintenance. This study reports on the effect of using 16mg/d v. 8 mg/d of buprenorphine on two year retention in an abstinence- oriented residential and outpatient bup/nx maintenance program.

METHODS

Patient Population

The patient population consisted of urban, low socio-economic status, uninsured patients with opiate dependence who met the DSM-IV criteria for Opiate Dependence and admission into the Rosary Hall - Alcohol and Drug Abuse Services Board of Cuyahoga County (ADASB) funded bup/nx treatment program.²⁵ All treatment services including pharmacotherapy were funded by a grant from the ADASB.²⁵

Eligible patients received preadmission demographic and clinical assessment of their addictive disorder, were admitted for 24-48 hours to the detoxification unit for buprenorphine induction to a goal dosage of 16mg daily.^{2, 24, 25} Patients were discharged to residential treatment for 4 and 8 weeks and then transitioned to an intensive outpatient treatment (IOP) level of care (three hours / day, four days / week for five weeks (20 sessions). After IOP, patients entered weekly aftercare monitoring for twelve weeks. Following aftercare, there was monthly follow-up in OBOMT clinic, with requirements of three AA meetings a week (including a "home group" and sponsor), and ongoing random urine toxicology screening.^{24, 26, 27} The ADASB grant covered a total of two years of participation per patient in this program. All aspects of the treatment program were considered

mandatory, and non-adherence resulted in referral back to the next higher level of care or administrative discharge if a pattern of non-adherence or positive toxicology testing emerged.

After 28 months of enrolling patients, there were substantial State budget cuts for Mental Health and Addiction treatment resulting in less funding for bup/nx and a mandatory dose decrease for all newly enrolled patients. Beginning in 2006 all grant-funded patients were treated with 8mg/d bup/nx rather than 16mg/d, resulting in two cohorts of patients differing on bup/nx dose.

Data Collection / Study Design

After receiving Human Subjects Committee Review from the Medical Center IRB, chart reviews of inpatient and outpatient records were conducted by a single reviewer. The charts were audited for demographic information including: age, gender and ethnicity, drug of choice, ancillary drug use history, induction dosage of buprenorphine and hospital discharge diagnosis. Data was obtained regarding a patient's completion of or discharge prior to each of the following program milestones: induction, residential treatment, IOP, aftercare, and one year of monthly OBOMT clinic. Chart audit information regarding completion of different levels of care was cross-checked against ADASB billing records to assure accuracy. All information was entered electronically, data-based, and numerically coded for export to a statistical analysis program.

Data Analysis

Demographic data and drug use history were analyzed using the student's t-test for continuous measures and the chi-square test for categorical variables. Treatment outcome results were compared using the chi-square test for retention at each change in treatment level of care.

RESULTS

Demographic, Drug Use and Treatment Characteristics

Our study population consisted of 157 uninsured low SES patients. Demographic, drug use, and selected treatment characteristics are displayed in **TABLE 1**. The study group was largely composed of middle-aged, male (73%), Caucasian (78%), heroin users (85%). The large majority had a history of poly-substance abuse (78%) and in addition to all currently having opioids as their drug of choice, most also at least intermittently used another non-opioid drug (66%). Table #1 also indicates that the two cohorts of patients in this study were not different from each other in pre-treatment characteristics including demographics, drug use, and prior treatment. The average length of residential treatment for our patients was 57 days with a standard deviation of 11 days and was similar for both cohorts (56 days s.d.=12, v. 59d s.d.=9).

Retention in Treatment by Induction Dose

Approximately 50% of the patients left the bup/nx treatment program at some point, either by dropping out or by being discharged for non-adherence. **TABLE 2** demonstrates the patient retention rate per treatment program milestone, comparing 16mg/d dose patients with 8mg/d dose patients. The retention rates at each level of care were very similar regardless of bup/nx dose. Of 157 patients starting residential treatment 89% in both groups completed this level of care. Of the 139 patients beginning the IOP counseling program, 77 and 78% in the 8mg and 16mg groups completed this level of care. Of the 108 patients beginning three months of weekly after care

sessions 77 and 78% of the 8mg and 16 mg cohorts respectively completed. Eighty-four patients began monthly OBOMT clinic monitoring after successfully completing each prior level of care, and 95 and 91% of the 8mg and 16mg groups completed at least one year of OBOMT clinic following aftercare. At 18 months following induction, 50% (35/70) of the 8mg cohort and 49.4% (43/87) of the 16mg cohort were retained in OBOMT.

DISCUSSION

This report takes advantage of a “natural experiment” where the public funding stream for a bup/nx OBOMT program was abruptly and arbitrarily changed resulting in two cohorts of patients on bup/nx maintenance differing only on bup/nx dose, one group on 16mg/d and one on 8mg/d. Treatment retention and opiate abstinence in each dose group were the same at each level of care, with the lower dose bup/nx proving to be just as effective as the higher dose. Demographic and pre-treatment drug use data indicate no differences between the two cohorts and the treatment program was not altered in any way other than decreasing the bup/nx daily dose. The program directors and the funding agency were quite concerned that this 50% decrease in daily dose would result in fewer patients applying for maintenance, fewer patients stabilizing on bup/nx, and more patients dropping out of treatment at each level of care. Clearly there were more subjective complaints from patients on the 8mg dose, but these subjective complaints did not translate into a lower retention rate. Finally, despite the change in dose the program continued to be overwhelmed with applicants.

Buprenorphine/naloxone (bup/nx) in office-based opioid maintenance therapy has been available for over eight years and much experience has been gained on practical issues related to the upper therapeutic range of prescribing including new recommendations from the manufacturer and over-sight agencies that support limiting typical dosing to 16mg/d or less. This is the first report to favorably compare the use of a lower dose of bup/nx with a 16mg/d dose. These results have implications for addiction treatment providers and for insurers with limited budgets or captive patient populations on OBOMT. After the induction and residential treatment phase, the largest cost of this bup/nx-assisted addiction treatment was the bup/nx- medication pharmacy cost. In this study the medication cost was able to be halved in the lower-dose cohort without adversely effecting treatment outcomes.

This report also provides data to inform the clinical debate about bup/nx maintenance-dose levels and the risk of diversion. Concern is widespread about substantial levels of diversion from “high dose” bup/nx clinics based upon anecdotal reports from patients in detoxification programs and law enforcement sources. Contrary to the recent experience with full mu-agonists, the increase in bup/nx diversion has not been accompanied by alarming reports of abuse, accidental over-dose and death.³⁰ However, the prescribing of excessive doses is of great concern to prescribers, industry, insurers and state and federal agencies and institutes. Certainly some patients with opioid addiction vigorously attempt to obtain the “highest effective” dose or even the “highest possible” dose of bup/nx, creating a difficult Dr-Pt relationship challenge for their prescribing physician. This report indicates that an abrupt and clinically arbitrary change in “ceiling” dose of bup/nx was met with patient complaints and disappointment, but not with any

evidence of adverse clinical outcomes. When combined with manufacturer current recommendations of doses at or below 16mg/d, this data can be re-enforcing to physicians who attempt to be prudent in dose selection.

There are several limitations regarding the data in this report and applicability to other settings. First, even though there are two different cohorts of patients in this report, it is at its core a case series of consecutively-enrolled patients in an OBOMT program who happened to receive different bup/nx doses. As such it carries the limitations and selection biases entailed in any case-series research. In fact, this case series is taken from a very particular bup/nx maintenance program that had exceptionally stringent requirements for treatment intensity and expectations for treatment adherence rather than a program with more harm-reduction treatment goals.^{25,29} The over-all retention rate of 50% at 18-24 months is lower than the much reported 60-80% range in other studies, and is likely related to several factors including the patient population's low socio-economic status, severity of the pre-treatment addictive disease, the stringency of the treatment program requirements to remain on bup/nx and the program expectations of adherence to a 12-step based abstinence program.²⁸

Additionally, it may be that the unusually high levels of psycho-social support and addiction treatment provided in this treatment program enabled patients to do well on lower doses of bup/nx, and that less structure and support for sobriety would not produce similar results at the lower bup/nx dose ranges. In reality these patients had no ability to pursue alternative sources for bup/nx – they had to be unemployed, uninsured and from a low enough socio-economic status to qualify for the grant program. The specific economic situation of our patient population may have contributed strongly to the similar outcomes between different bup/nx doses. Other communities may have different treatment needs and different populations requiring care, so this treatment model and the outcomes that we achieved may not be applicable across communities.

Information about different aspects of patient treatment with OBOMT continues to emerge from the American bup/nx opioid addiction treatment experience. This report provides important results for publicly funded treatment providers and insurers who provide for low socio-economic status opiate-addicted patient populations. These results also can inform the debate about the clinical justification for high dose (greater than 24mg/d) bup/nx prescribing, can address concerns about diversion and support providing long-term bup/nx maintenance within a reasonably prudent dose range.

TABLE 1. Demographic and Drug Use Data

	Total (n=157)	Induced on 8 mg/day (n=70)	Induced on 16 mg/day (n=87)	p
	<i>(n) or (SD)</i>	<i>(n) or (SD)</i>	<i>(n) or (SD)</i>	
Age	38 (11)	38 (12)	38 (11)	0.916
Sex				
<i>Male</i>	72.9% (113)	72.3% (47)	73.3% (66)	1.000
Ethnicity				
<i>Asian</i>	0.7% (1)	0.0% (0)	1.1% (1)	0.803
<i>Black</i>	15.5% (24)	13.9% (9)	16.7% (15)	0.803
<i>Caucasian</i>	78.0% (121)	80.0% (52)	76.7% (69)	0.803
<i>Hispanic</i>	5.8% (9)	6.1% (4)	5.5% (5)	0.803
Drug of Choice				
<i>Heroin</i>	84.5% (131)	84.6% (55)	84.5% (76)	0.644
<i>Rx</i>	1.9% (3)	3.1% (2)	1.1% (1)	0.644
<i>Both</i>	13.6% (21)	12.3% (8)	14.4% (13)	0.644
Polysubstance Abuse	78.1% (121)	81.5% (53)	75.6% (68)	0.434
Secondary Drug/s				
<i>Any</i>	65.8% (102)	64.6% (42)	66.7% (60)	0.864
<i>Alcohol</i>	31.6% (49)	30.8% (20)	32.2% (29)	0.863
<i>Cannabis</i>	20.0% (31)	27.7% (18)	14.4% (13)	0.066
<i>Cocaine</i>	36.8% (57)	33.9% (22)	38.9% (35)	0.613
<i>Other</i>	12.9% (20)	9.2% (6)	15.6% (14)	0.333

TABLE 2. Retention in treatment

	Total	8 mg/d	16 mg/d
	starting this LOC	$\frac{\text{Finish LOC}}{\text{Start LOC}}$	$\frac{\text{Finish LOC}}{\text{Start LOC}}$
Residential TX	157	62/70 (89%)	77/87 (89%)
IOP TX	139	48/62 (77%)	60/77 (78%)
Aftercare TX	108	37/48 (77%)	47/60 (78%)
End of one year of Bup/Nx Clinic TX	84	35/37 (95%)	43/47 (91%)
End of ADASB grant (24 months)	52 (25*)	7/9 (78%)	32/43 (74%)

* Patients still in this LOC at time of data collection



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Short communication

Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy

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ABSTRACT

Background: Buprenorphine/naloxone was approved by the FDA for office-based opioid maintenance therapy (OMT), with little long-term follow-up data from actual office-based practice. 18-Month outcome data on the office-based use of buprenorphine/naloxone (bup/nx) and the impact of socioeconomic status and other patient characteristics on the duration and clinical effects of bup/nx are reported.

Methods: This retrospective chart review and cross-sectional telephone interview provide treatment retention of opioid-dependent patients receiving bup/nx-OMT in an office-based setting. 176 opioid-dependent patients from two different socioeconomic groups (high and low SES) were begun on bup/nx, started intensive outpatient treatment, and followed-up after a minimum of 18 months (18–42 months) by telephone interview to assess treatment outcome.

Results: 110 subjects (67%) completed the interview, 77% remained on bup/nx with no difference in retention between high and low SES groups. Those on bup/nx at follow-up were more likely to report abstinence, to be affiliated with 12-step recovery, to be employed and to have improved functional status. **Conclusions:** Bup/nx-OMT is a viable treatment option and when coupled with a required abstinence oriented addiction counseling program is effective in promoting abstinence, self-help group attendance, occupational stability, and improved psychosocial outcomes in both low SES and high SES patient populations over an 18–42-month period.

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1. Introduction

The buprenorphine/naloxone (bup/nx) sublingual tablet was approved by the FDA in 2002 and in early 2003 became available for use in the United States for office-based opioid maintenance therapy (OMT) for opioid-dependent patients (Johnson et al., 2003). This enabled major changes in the way opiate addiction is treated in the United States (Fiellin and O'Connor, 2002b; Fiellin et al., 2001; Jaffe and O'Keefe, 2003). Substantial pre-release research demonstrated the safety, efficacy and comparability of bup/nx with previous forms of OMT like methadone. bup/nx also appears to have a good safety profile compared to methadone maintenance including a decreased risk with overdose or diversion, ease of dosage titration, possible ease and brevity for tapering, and possibly a decreased impact on the patient's cognitive function (Carrier et

al., 2006; Fiellin et al., 2004; Fiellin and O'Connor, 2002a; Fudala et al., 2003; Harris et al., 2000; Jasinski et al., 1978; Johnson et al., 2000, 1992; Ling et al., 1998, 1996; Mattick et al., 2003; Mendelson and Jones, 2003; Simoens et al., 2005; Strain et al., 1994; Walsh and Eissenberg, 2003).

This favorable safety profile of buprenorphine and the ability to move opioid agonist therapy to an office rather than addiction clinic setting has resulted in significant prescribing and a growing body of post-release bup/nx research and clinical experience (Bouchez and Vignau, 1998). Post-release studies have shown bup/nx to significantly reduce opioid withdrawal symptoms, improve retention in substance abuse treatment, and improve treatment completion roughly similar to methadone treatment (Amass et al., 1994; Caldiero et al., 2006; Fiellin et al., 2002; Gibson et al., 2003; Johnson et al., 1995; Krook et al., 2002; Moore et al., 2007; Stein et al., 2005; Auriacombe et al., 1994; Giacomuzzi et al., 2005; Johnson et al., 2000; Kakko et al., 2003; Kosten et al., 1993; Mattick et al., 2003; O'Connor et al., 1998; Strain et al., 1994).

There are several areas in which more research on OMT with bup/nx is needed including; outcomes with use in the actual private practice office setting, data on greater than 1 year follow-up

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(Alford et al., 2007; Fhima et al., 2001; Kornor et al., 2007; McLellan et al., 2000), and pre-induction patient characteristics as a predictor of long-term retention in treatment (Marsch et al., 2005). In addition very few studies have examined the long-term effectiveness of bup/nx in uninsured and underinsured populations (low socioeconomic status or low SES) (Mintzer et al., 2007).

This report provides outcome data on a large number of bup/nx maintained patients in an urban office setting with cross-sectional follow-up at a minimum of 18 months post-induction. Data include the impact of pre-treatment patient variables on patient outcomes including demographic, drug and alcohol use histories and socioeconomic status. The primary objective of the study was to assess retention on bup/nx treatment, drug use, morbidity from addictive disease and sobriety rates in 176 patients at least 18 months post-induction. The secondary objective was to analyze the impact of pre-induction patient characteristics including SES on the duration and outcome of bup/nx treatment at least 18 months post-induction.

2. Methods

The patient population consisted of 176 consecutively admitted opioid dependent adults age 19-65 who met the criteria for admission into the bup/nx treatment program (DSM-IV Opiate Dependence, multiple prior failed attempts at abstinence, lack of additional uncontrolled axis I diagnosis/psychosis, not homeless). Patients were admitted over a 30-month period of time. Initially only privately insured or full self-pay patients (the high SES group) were admitted to the bup/nx OMP. Starting in 2005 indigent and uninsured patients (the low SES group) were admitted under a treatment grant from the County Alcohol and Drug Abuse Services Board (ADASB). All patients had standardized addiction assessments performed and were induced on bup/nx doses between 12 and 16 mg/day (Caldiero et al., 2006).

Treatment was divided into a "primary phase" where all patients were followed by the investigators and an ongoing "outpatient phase" where many patients were referred to outlying primary care follow-up due to patient cap constraints. Primary treatment involved a 23-48 h inpatient admission for induction, participation in 5 weeks of intensive outpatient (IOP) counseling (3 h/day, 4 days/week), followed by 12 weeks of weekly once aftercare sessions (Caldiero et al., 2006). Following primary treatment, bup/nx office follow-up involved monthly visits with ongoing 12-step meeting attendance (three each week) and quarterly toxicology testing. The ADASB grant required low SES patients to participate in 1-2 months of half-way house level of care between the induction and IOP treatment phase.

Full adherence (attendance, participation and abstinence) to each level of treatment was required. Non-adherence or substance use resulted in referral back to the next highest level of care. Repeated substance use or non-adherence resulted in taper off of bup/nx and discharge.

After obtaining Human Subjects Committee review from the medical center IRB, chart reviews from hospital and outpatient clinic records were conducted by two Addiction Psychiatry Fellows using a standardized chart review form. A Fellow attempted to phone each patient at a minimum of 18 months (and a maximum of 42 months) after induction. Informed consent was obtained and the structured interview was conducted, including questions on opioid and other alcohol or drug use, continuous bup/nx medication use, and social, role and occupational function from the Shortened Inventory of Problems (SIP-AD).

Chart review and telephone interview forms were scanned into an SPSS database. Simultaneous equations were modeled to test hypothesized interrelationships between patient factors, treatment factors, and outcomes at least 18 months after bup/nx induction. Retention in bup/nx treatment was modeled by discrete time survival analysis (Muthén, 2001).

3. Results

Over 30 months 176 subjects were inducted on bup/nx and eligible for follow-up. 33% were female; 73% Caucasian, 21% Black, and 5% Hispanic, consistent with the overall racial characteristics of opioid-dependent patients in the region. 110 of 176 (63%) completed the follow-up telephone interview at least 18 months post-induction. Table 1 contains basic pre-induction demographic, drug use history, medical, legal, and psychosocial data. There were no significant differences in the baseline characteristic variables between subjects who completed the telephone interview and those who did not except that non-completers were more likely to have an arrest history ($\chi^2_{11} = 4.96, p = 0.03$).

Table 1

Demographic, drug use, and other intake variables shown for subjects initially enrolled in the study and the subset of those individuals available for follow-up.

Variable	Total (N = 176)	Subjects completing telephone interview (N = 110)
Ethnicity		
African American	37 (21%)	23 (21%)
Hispanic	8 (5%)	4 (4%)
White, non-Hispanic	129 (73%)	81 (74%)
Other	2 (1%)	2 (1%)
Female	58 (32%)	35 (32%)
Insurance status		
Insurance	72 (41%)	40 (37%)
Medicaid	10 (5%)	6 (5%)
Medicare	3 (2%)	2 (2%)
Self-pay	91 (52%)	62 (56%)
Significant other	76 (58%)	45 (66%)
Significant other using	15 (12%)	9 (13%)
Prescription opioid use	21 (12%)	12 (11%)
Route of administration		
Injection	130 (74%)	78 (71%)
Nasal	23 (13%)	18 (16%)
Oral	23 (13%)	14 (13%)
Medical history		
Abscess	13 (10%)	5 (8%)
Bacterial endocarditis	1 (1%)	0 (0%)
Depression	73 (41%)	43 (39%)
Hepatitis C	44 (34%)	20 (30%)
HIV	1 (1%)	0 (0%)
Injury	34 (27%)	13 (20%)
Overdose	5 (4%)	3 (5%)
Prior psychiatric treatment	69 (39%)	42 (38%)
Legal history		
Arrest	45 (35%)	17 (26%)
Prior legal problems	108 (61%)	66 (60%)

Table 2 presents data on the 110 follow-up patients regarding continuous bup/nx therapy, substance use, AA affiliation, employment, psychosocial functioning and several other demographic, socioeconomic, medical and legal variables. The majority of patients completing phone follow-up were Caucasian (73%), male (67%), and had a significant other (58%). 52% of subjects were low SES, 48% were high SES, and 88% were heroin users with 74% reporting I.V. use. Depression (41%) and hepatitis C (34%) were the most common medical comorbidities and 39% reported prior psychiatric treatment. 61% of patients reported prior legal problems with 35% having been incarcerated.

At follow-up, 77% of subjects reported that they had continuously remained on bup/nx. Patients on continuous bup/nx were significantly less likely to report using any substance ($\chi^2 = 6.26, p = 0.012$) and were less likely to report using heroin ($\chi^2 = 8.1, p = 0.004$). Continued bup/nx patients were significantly more likely to report AA affiliation ($\chi^2 = 5.49, p = 0.019$), including a "home group", a "sponsor", and attending 3+ 12-step meetings per week ($\chi^2 = 4.72, p = 0.029$). Those on bup/nx were significantly more likely to have been employed at baseline ($\chi^2 = 4.92, p = 0.027$) and at follow-up ($\chi^2 = 4.89, p = 0.027$).

Regarding psychosocial parameters, patients continuously on bup/nx were less likely to reported damaging a close relationship ($\chi^2 = 6.07, p = 0.014$), doing regretful or impulsive things ($\chi^2 = 4.89, p = 0.027$), hurting family ($\chi^2 = 8.52, p = 0.004$), experiencing negative personality changes ($\chi^2 = 4.43, 0.035$), failing to do things expected of them ($\chi^2 = 9.54, p = 0.002$), taking foolish risks ($\chi^2 = 11.36, p = 0.0008$), being unhappy ($\chi^2 = 9.27, p = 0.002$), and having money problems ($\chi^2 = 5.97, p = 0.015$). The study design did not allow these results to be controlled for opioid abstinence.

Table 2
Addiction related Intake and outcome variables by insurance status and continued bup/nx use at follow-up.

Variable (endorsed)	Total (N = 110)	Uninsured		Insured		Insured ^a		bup/nx at follow-up ^b	
		No (N = 12)	Yes (N = 50)	No (N = 13)	Yes (N = 35)	44% (48/110)		77% (85/110)	
Using bup/nx at follow-up						χ^2	P	χ^2	P
<i>Intake variables</i>									
Minority	27/110 (25%)	1 (8%)	9 (18%)	6 (46%)	11 (31%)	6.82	0.009	NS	
Female	35/110 (32%)	3 (25%)	12 (24%)	5 (38%)	15 (43%)	NS		NS	
Significant other	45/68 (66%)	2 (29%)	7 (44%)	11 (85%)	25 (78%)	12.4	0.0004	NS	
Who is using	9/67 (13%)	0 (0%)	1 (7%)	2 (15%)	6 (19%)	NS		NS	
Prescription opioid use	12/107 (11%)	0 (0%)	3 (6%)	2 (15%)	7 (20%)	NS		3.13	0.0768 ^c
Route: injection	78/110 (71%)	10 (83%)	41 (82%)	9 (69%)	18 (51%)	NS		NS	
Medical comorbidity	21/64 (33%)	3 (50%)	7 (54%)	4 (31%)	7 (22%)	NS		NS	
Hepatitis C	20/64 (31%)	2 (33%)	7 (54%)	4 (31%)	7 (22%)	NS		NS	
Abscess	5/63 (8%)	1 (17%)	2 (15%)	0 (0%)	2 (6%)	2.77	0.0963 ^c	NS	
Overdose	3/66 (5%)	0 (0%)	1 (7%)	0 (0%)	2 (6%)	NS		NS	
Depression	43/110 (39%)	7 (58%)	16 (32%)	6 (46%)	14 (40%)	NS		NS	
History of psychiatric treatment	42/110 (38%)	5 (42%)	18 (36%)	6 (46%)	13 (37%)	NS		NS	
Legal comorbidity	69/106 (65%)	9 (82%)	32 (67%)	7 (54%)	21 (62%)	NS		NS	
Arrest history	17/63 (27%)	4 (67%)	4 (31%)	3 (23%)	6 (19%)	NS		NS	
Any legal problems	66/106 (62%)	9 (82%)	32 (67%)	6 (46%)	19 (56%)	3.01	0.0827 ^c	NS	
<i>Outcome variables</i>									
Substance use	16/110 (15%)	4 (33%)	7 (14%)	4 (31%)	1 (3%)	4.09	0.0432	6.26	0.0123
Alcohol	8/110 (7%)	3 (25%)	4 (8%)	1 (8%)	0 (0%)	4.95	0.026	3.8	0.0513 ^c
Heroin	14/110 (13%)	4 (33%)	7 (14%)	3 (23%)	0 (0%)	7.97	0.0047	8.1	0.0044
Cocaine	8/110 (7%)	1 (8%)	5 (10%)	1 (8%)	1 (3%)	NS		NS	
AA affiliated	95/110 (86%)	9 (75%)	46 (92%)	7 (54%)	33 (94%)	NS		5.49	0.0191
Home group	83/110 (76%)	8 (67%)	41 (84%)	4 (31%)	30 (86%)	NS		3.40	0.0654 ^c
Has sponsor	88/110 (80%)	9 (75%)	43 (86%)	5 (38%)	31 (89%)	NS		4.72	0.0298
3+ meetings/week	73/110 (66%)	6 (50%)	38 (76%)	6 (46%)	23 (66%)	NS		NS	
<i>Employment characteristics</i>									
Employed—baseline	26/110 (24%)	1 (8%)	6 (12%)	4 (31%)	15 (43%)	4.84	0.0278	4.92	0.0266
Employed—follow-up	64/110 (58%)	2 (17%)	32 (64%)	7 (54%)	23 (66%)	NS		4.89	0.0271
Employment changes	n/a	n/a	n/a	n/a	n/a	NS		2.84	0.0918 ^c
Still not employed	43/110 (39%)	10 (83%)	18 (36%)	5 (38%)	10 (29%)	n/a		n/a	
Still employed	23/110 (21%)	1 (8%)	6 (12%)	3 (23%)	13 (37%)	n/a		n/a	
Newly employed	3/110 (3%)	1 (8%)	26 (52%)	4 (31%)	10 (29%)	n/a		n/a	
No longer employed	41/110 (37%)	0 (0%)	0 (0%)	11 (8%)	2 (6%)	n/a		n/a	

Analyses control for baseline medical and legal comorbidity. Uninsured = Self-pay classification; Insured = Insured, Medicaid, Medicare (Medicaid and Medicare are considered insured by St. Vincent Charity Hospital standards). NS = not significant ($\alpha = p < 0.05$).

^a Test statistics for group difference across insured and uninsured groups.

^b Test statistics for group difference across those who did and those who did not report current bup/nx use at follow-up.

^c Trend level observation ($p < 0.1$).

SES sub-group analysis indicated that high SES subjects were more likely to be from a minority background ($\chi^2 = 6.82, p = 0.009$) and were more likely to have a significant other ($\chi^2 = 12.36, p = 0.0004$). High SES subjects were more likely to be employed at baseline ($\chi^2 = 4.84, p = 0.028$), but not at follow-up. Low SES subjects were more likely to report still being on bup/nx at the time of follow-up. There was more substance use at follow-up in the low SES subjects ($\chi^2 = 4.09, p = 0.0432$).

4. Discussion

This study is one of the largest case series to date to report outcomes of office-based bup/nx maintenance with minimum 18-month follow-up data. The goals of the present study were to determine the proportion of subjects still using bup/nx at follow-up, to compare levels of functioning in continuously maintained bup/nx patients with those who dropped out, and to assess whether pre-treatment variables including SES were predictive of treatment retention.

At between 18 months and 4 years of follow-up, 85 of 110 of subjects contacted were still using bup/nx (77%), indicating that bup/nx can clearly be an effective long-term adjunct to a compre-

hensive abstinence oriented, 12-step treatment program. Subjects who remained on bup/nx reported dramatic improvement in many domains of quality of life and measures of sobriety when compared to drop outs including: less substance use, fewer psychosocial complications of addiction, more AA affiliation activities, and increased employment at follow-up. The major reason for drop out or discontinuation from bup/nx maintenance was failure to fully adhere with the abstinence based 12-step treatment or repeated evidence of substance use. Thus improved psychosocial functioning in bup/nx maintained patients was likely due to their marked decreased rate of substance use and not solely due to the bup/nx. Increasing levels of employment for patients remaining on bup/nx is very important given that long-term bup/nx therapy, especially if that therapy involves some degree of public funding, can hinge on a return to gainful employment and medication funding independence.

A secondary goal was to examine whether pre-treatment characteristics were associated with bup/nx retention. Factors associated with improved retention were being employed at entry into the study and the use of prescription opioids rather than heroin. This supports the prior observation that bup/nx outcomes may be improved in prescription opioid abusers over heroin abusers (Moore et al., 2007). A pre-treatment variable of spe-

cial interest was patient SES. Slightly more low SES patients remained on bup/nx, the low SES patients demonstrated similar improvements in quality of life measures, and greater increases in employment status when compared to the high SES group. Despite the better retention in low SES patients and the fact that they received more treatment in the form of a half-way house residential stay, they were also slightly more likely (8%) to report substance use and hence relapse of addictive disease. Clearly, low SES patients can benefit greatly from bup/nx maintenance when combined with quality addiction counseling treatment.

This low SES patient group is a different population than reported on in other bup/nx studies. Previous reports on low SES groups have examined outcomes in homeless patient populations (Alford et al., 2007; Fiellin et al., 2006; Stein et al., 2005). All of the low SES patients in this study had stable housing, but were uninsured, mostly unemployed (89%), unmarried (86%), injection drug users (82%). None of our low SES patients could afford either the medications or the costs the treatment at entry to the program. The low SES patients in this study represent a large group of the US drug abusing population who are uninsured but are not truly homeless. As such they are a unique and important group to study.

This study has several important limitations. The study population is a clinical case series and a convenience sample derived from a clinical cohort stabilized on bup/nx as part of a private insurance and publicly funded treatment program, and was not part of any planned research protocol. The study was not prospective, with results obtained via retrospective chart review and cross-sectional telephone interview. Finally, while one strength of this study was its different SES patient populations, an important weakness was the necessity for different intensity of addiction treatment between the two groups. Because treatment of indigent subjects was publicly funded, these individuals were required by the funding agency to undergo 4-8 weeks of half-way house treatment that was not provided to any of the insured subjects. This created two potential biases: a treatment bias whereby indigent patients received longer and more intensive substance abuse treatment, and potentially a selection bias since this half-way house treatment was mandated and thus low SES patients unable or unwilling to go into the residential setting were not initiated on bup/nx.

Despite these limitations we believe the results of this study confirm that bup/nx can be effectively combined with a rigorous abstinence based 12-step treatment program and produce long-term improvements in sobriety and quality of life. These beneficial effects appear to be evident in low SES and high SES patient populations.

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Contributors

T. Parran consulted on the study development, supervised data collection, and wrote the final manuscript. C. Adelman developed the study design, provided clinical supervision and medical records access, supervised the IRB proposal and supervised all data collection. A. Mace compiled all data and wrote the initial draft of the report. M. Pagano provided data supervision, data analysis, and manuscript writing and editing. R. Ionescu provided data supervision, data analysis, and manuscript writing and editing. B. Merkin

proposed the study, wrote the IRB protocol, developed the chart review forms, and edited the final manuscript. R. Defraco provided chart review services and conducted the phone interviews.

Conflict of interest

T. Parran is a member of the Speakers Bureau for ReckittBinckiser and a Buprenorphine Course Director and Faculty Member for ASAM, and a faculty mentor on the ASAM PCSS Buprenorphine web-service. C. Adelman is a member of the Speakers Bureau for ReckittBinckiser and a Buprenorphine Course Faculty Member for ASAM. B. Merkin has no disclosures to provide. R. Defraco has no disclosures to provide. A. Mace has no disclosure to provide. M. Pagano has no disclosures to provide. R. Ionescu has no disclosures to provide.

Uncited references

Bickel et al. (1997), Blanchard et al. (2003) and U.S. Dept. of Health and Human Services (2006).

References

- Alford, D.P., LaBelle, C.T., Richardson, J.M., O'Connell, J.J., Hohl, C.A., Cheng, D.M., Samet, J.H., 2007. Treating homeless opioid dependent patients with buprenorphine in an office-based setting. *J. Gen. Intern. Med.* 22, 171-176.
- Amass, L., Bickel, W.K., Higgins, S.T., Hughes, J.R., 1994. A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. *J. Addict. Dis.* 13, 33-45.
- Auriacombe, M., Grabot, D., Daulouede, J.P., Vergnolle, J.P., O'Brien, C., Tignol, J., 1994. A naturalistic follow-up study of French-speaking opiate-maintained heroin-addicted patients: effect on biopsychosocial status. *J. Subst. Abuse Treat.* 11, 565-568.
- Bickel, W.K., Amass, L., Higgins, S.T., Badger, G.J., Esch, R.A., 1997. Effects of adding behavioral treatment to opioid detoxification with buprenorphine. *J. Consult. Clin. Psychol.* 65, 803-810.
- Blanchard, K.A., Morgenstern, J., Morgan, T.J., Lobouvie, E.W., Bux, D.A., 2003. Assessing consequences of substance use: psychometric properties of the inventory of drug use consequences. *Psychol. Addict. Behav.* 17, 328-331.
- Bouchez, J., Vignau, J., 1998. The French experience—the pharmacist, general practitioner and patient perspective. *Eur. Addict. Res.* 1 (4 Suppl.), 19-23.
- Caldiero, R.M., Parran Jr., T.V., Adelman, C.L., Piche, B., 2006. Inpatient initiation of buprenorphine maintenance vs. detoxification: can retention of opioid-dependent patients in outpatient counseling be improved? *Am. J. Addict.* 15, 1-7.
- Carrieri, M.P., Amass, L., Lucas, G.M., Vlahov, D., Wodak, A., Woody, G.E., 2006. Buprenorphine use: the international experience. *Clin. Infect. Dis.* 43 (Suppl 4), S197-215.
- Fhima, A., Henrion, R., Lowenstein, W., Charpak, Y., 2001. Two-year follow-up of an opioid-user cohort treated with high-dose buprenorphine (Subutex). *Ann. Med. Intern. (Paris)* 152 (Suppl 3), IS26-36.
- Fiellin, D.A., Kleber, H., Trumble-Hejduk, J.G., McLellan, A.T., Kosten, T.R., 2004. Consensus statement on office-based treatment of opioid dependence using buprenorphine. *J. Subst. Abuse Treat.* 27, 153-159.
- Fiellin, D.A., O'Connor, P.G., 2002a. Clinical practice. Office-based treatment of opioid-dependent patients. *N. Engl. J. Med.* 347, 817.
- Fiellin, D.A., O'Connor, P.G., 2002b. New federal initiatives to enhance the medical treatment of opioid dependence. *Ann. Intern. Med.* 137, 688-692.
- Fiellin, D.A., Pantalon, M.V., Chawarski, M.C., Moore, B.A., Sullivan, L.E., O'Connor, P.G., Schottenfeld, R.S., 2006. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N. Engl. J. Med.* 355, 365-374.
- Fiellin, D.A., Pantalon, M.V., Pakes, J.P., O'Connor, P.G., Chawarski, M., Schottenfeld, R.S., 2002. Treatment of heroin dependence with buprenorphine in primary care. *Am. J. Drug Alcohol. Abuse* 28, 231-241.
- Fiellin, D.A., Rosenheck, R.A., Kosten, T.R., 2001. Office-based treatment for opioid dependence: reaching new patient populations. *Am. J. Psychiatry* 158, 1200-1204.
- Fudala, P.J., Bridge, T.P., Herbert, S., Williford, W.O., Chiang, C.N., Jones, K., Collins, J., Raisch, D., Casadonte, P., Goldsmith, R.J., Ling, W., Malkerker, U., McNicholas, L., Renner, J., Stine, S., Tusel, D., 2003. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N. Engl. J. Med.* 349, 949-958.
- Giacomuzzi, S.M., Ertl, M., Kemmler, G., Riemer, Y., Vigl, A., 2005. Sublingual buprenorphine and methadone maintenance treatment: a three-year follow-up of quality of life assessment. *Sci. World J.* 5, 452-468.
- Gibson, A.E., Doran, C.M., Bell, J.R., Ryan, A., Lintzeris, N., 2003. A comparison of buprenorphine treatment in clinic and primary care settings: a randomised trial. *Med. J. Aust.* 179, 38-42.

- 333 Harris, D.S., Jones, R.T., Welm, S., Upton, R.A., Lin, E., Mendelson, J., 2000. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. *Drug Alcohol. Depend.* 61, 85-94. 374
- 334 375
- 335 376
- 336 Jaffe, J.H., O'Keefe, C., 2003. From morphine clinics to buprenorphine: regulating 377
- 337 opioid agonist treatment of addiction in the United States. *Drug Alcohol. Depend.* 378
- 338 70, S3-S11. 379
- 339 Jasinski, D.R., Pevnick, J.S., Griffith, J.D., 1978. Human pharmacology and abuse 380
- 340 potential of the analgesic buprenorphine: a potential agent for treating narcotic 381
- 341 addiction. *Arch. Gen. Psychiatry* 35, 501-516. 382
- 342 Johnson, R.E., Chutuape, M.A., Strain, E.C., Walsh, S.L., Stitzer, M.L., Bigelow, G.E., 383
- 343 2000. A comparison of levomethadyl acetate, buprenorphine, and methadone 384
- 344 for opioid dependence. *N. Engl. J. Med.* 343, 1290-1297. 385
- 345 Johnson, R.E., Eissenberg, T., Stitzer, M.L., Strain, E.C., Liebson, I.A., Bigelow, G.E., 386
- 346 1995. A placebo controlled clinical trial of buprenorphine as a treatment for 387
- 347 opioid dependence. *Drug Alcohol. Depend.* 40, 17-25. 388
- 348 Johnson, R.E., Jaffe, J.H., Fudala, P.J., 1992. A controlled trial of buprenorphine treat- 389
- 349 ment for opioid dependence. *JAMA* 267, 2750-2755. 390
- 350 Johnson, R.E., Strain, E.C., Amass, L., 2003. Buprenorphine: how to use it right. *Drug 391*
- 351 *Alcohol. Depend.* 70, S59-77. 392
- 352 Kakko, J., Svanborg, K.D., Kreek, M.J., Heilig, M., 2003. 1-year retention and social 393
- 353 function after buprenorphine-assisted relapse prevention treatment for heroin 394
- 354 dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 361, 395
- 355 662-668. 396
- 356 Kornor, H., Waal, H., Sandvik, L., 2007. Time-limited buprenorphine replacement 397
- 357 therapy for opioid dependence: 2-year follow-up outcomes in relation to pro- 398
- 358 gramme completion and current agonist therapy status. *Drug Alcohol. Rev.* 26, 399
- 359 135-141. 400
- 360 Kosten, T.R., Schottenfeld, R., Ziedonis, D., Falcioni, J., 1993. Buprenorphine ver- 401
- 361 sus methadone maintenance for opioid dependence. *J. Nerv. Ment. Dis.* 181, 402
- 362 358-364. 403
- 363 Krook, A.L., Brors, O., Dahlberg, J., Grouff, K., Magnus, P., Roysamb, E., Waal, H., 2002. 404
- 364 A placebo-controlled study of high dose buprenorphine in opiate dependents 405
- 365 waiting for medication-assisted rehabilitation in Oslo, Norway. *Addiction* 97, 406
- 366 533-542. 407
- 367 Ling, W., Charuvastra, C., Collins, J.F., Batki, S., Brown Jr., L.S., Kintaudi, P., Wes- 408
- 368 son, D.R., McNicholas, L., Tusel, D.J., Malkernek, U., Renner Jr., J.A., Santos, E., 409
- 369 Casadonte, P., Fye, C., Stine, S., Wang, R.I., Segal, D., 1998. Buprenorphine main- 410
- 370 tenance treatment of opiate dependence: a multicenter, randomized clinical trial. 411
- 371 *Addiction* 93, 475-486. 412
- 372 Ling, W., Wesson, D.R., Charuvastra, C., Klett, C.J., 1996. A controlled trial comparing 413
- 373 buprenorphine and methadone maintenance in opioid dependence. *Arch. Gen. Psychiatry* 53, 401-407.
- Marsch, L.A., Stephens, M.A.C., Mudric, T., Strain, E.C., Bigelow, G.E., Johnson, R.E., 2005. Predictors of outcome in LAAM, buprenorphine, and methadone treatment for opioid dependence. *Exp. Clin. Psychopharmacol.* 13, 293-302.
- Mattick, R.P., Ali, R., White, J.M., O'Brien, S., Wolk, S., Danz, C., 2003. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction* 98, 441-452.
- McLellan, A.T., Lewis, D.C., O'Brien, C.P., Kleber, H.D., 2000. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 284, 1689-1695.
- Mendelson, J., Jones, R.T., 2003. Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: why the 4:1 ratio for treatment? *Drug Alcohol. Depend.* 70, S29-S37.
- Mintzer, L.L., Eisenberg, M., Terra, M., MacVane, C., Himmelstein, D.U., Woolhandler, S., 2007. Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings. *Ann. Fam. Med.* 5, 146-150.
- Moore, B.A., Fiellin, D.A., Barry, D.T., Sullivan, L.E., Chawarski, M.C., O'Connor, P.G., Schottenfeld, R.S., 2007. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *J. Gen. Intern. Med.* 22, 527-530.
- Muthén, B.O.M.L.K., 2001. *Mplus User's Guide*. Muthén & Muthén, Los Angeles, CA.
- O'Connor, P.G., Oliveto, A.H., Shi, J.M., Triffleman, E.G., Carroll, K.M., Kosten, T.R., Rounsaville, B.J., Pakes, J.A., Schottenfeld, R.S., 1998. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *Am. J. Med.* 105, 100-105.
- Simoens, S., Matheson, C., Bond, C., Inkster, K., Ludbrook, A., 2005. The effectiveness of community maintenance with methadone or buprenorphine for treating opiate dependence. *Br. J. Gen. Pract.* 55, 139-146.
- Stein, M.D., Cioe, P., Friedmann, P.D., 2005. Buprenorphine retention in primary care. *J. Gen. Intern. Med.* 20, 1038-1041.
- Strain, E.C., Stitzer, M.L., Liebson, I.A., Bigelow, G.E., 1994. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am. J. Psychiatry* 151, 1025-1030.
- U.S. Dept. of Health and Human Services, S.A.a.M.H.S.A., Office of Applied Studies, 2006-10-17. NATIONAL SURVEY ON DRUG USE AND HEALTH, 2003 [Computer File]. ICPSR04138-v2. Research Triangle Institute, Research Triangle Park, NC, 2004 [Producer]. Inter-University Consortium for Political and Social Research, Ann Arbor, MI [Distributor].
- Walsh, S.L., Eissenberg, T., 2003. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug Alcohol. Depend.* 70, S13-27.

Attachment I

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WHAT IS BUPRENORPHINE?

Buprenorphine is a medication used to treat patients who are addicted to opioids such as heroin, morphine, Oxycontin, Vicodin and other opioids. It is a semi-synthetic opioid derived from thebaine, a naturally occurring alkaloid of the opium poppy, *Papaver somniferum*. It is classified by the United States Drug Enforcement Administration (DEA) as a Schedule III narcotic.

Buprenorphine has three United States Food and Drug Administration (FDA) indications: opioid detoxification, opioid maintenance, and pain management. Opioid **detoxification** describes the process in which a physically dependent individual is gradually tapered off all opioids, typically over a period of days to weeks. Opioid **maintenance** is the long-term (typically months to years) substitution with a regulated opioid with the goal of discontinuing or substantially decreasing illicit opioid use. The liquid form of buprenorphine (BUPRENEX) and transdermal patch (BUTRANS) are approved for pain management.

HOW DOES BUPRENORPHINE WORK?

Buprenorphine is a partial agonist that is active at the mu opioid receptors. This means that it attaches to the same receptor as other opioids but that it does not —turn on|| or activate the receptor as much as other opioids do (See Figures 1 and 2). In addition to the primary effects on the *mu* opioid receptor, buprenorphine also appears to act as an antagonist at the *kappa* opioid receptor (possibly involved with spinal analgesia and anti-dysphoric effects), as an agonist at the *delta* receptor (clinical significance uncertain) and as a partial agonist at the opioid-receptor-like 1 (ORL-1).

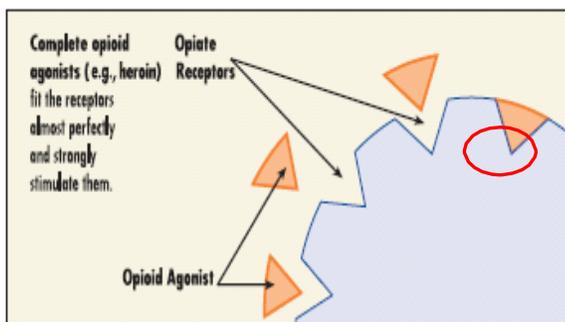


Fig. 1. Opiate receptors with full-agonist opioid (e.g., heroin). Complete opioid agonists fit receptors almost perfectly and strongly stimulate them. Full agonists initially produce a strong euphoric effect. After prolonged use, tolerance and physical dependence can develop, and people continue to abuse opioids to avoid withdrawal symptoms.

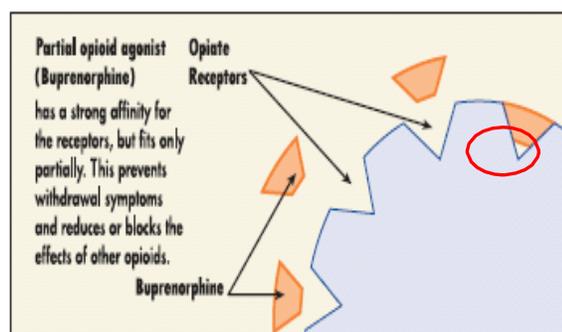
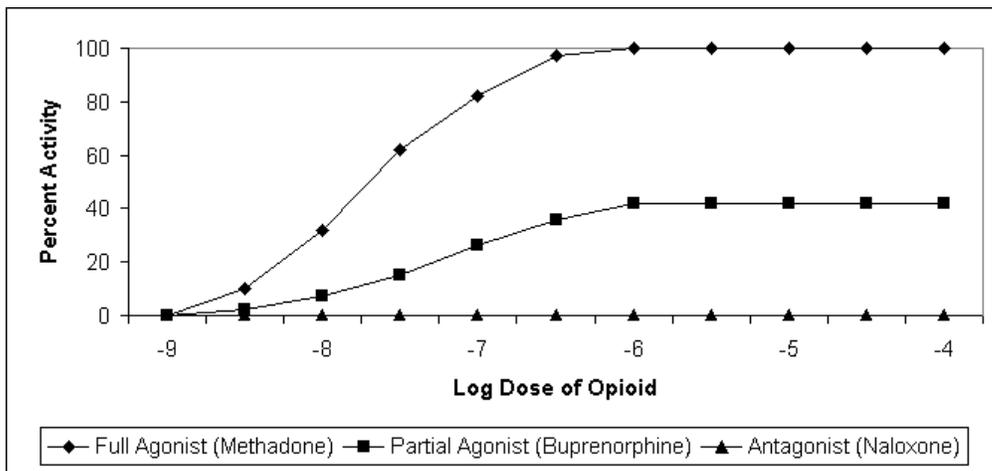


Fig. 2. Opiate receptors with partial-agonist opioid (buprenorphine). Buprenorphine has a strong affinity for the receptors but fits only partially, so it stimulates the receptors to a lesser degree while effectively blocking other opioids from attaching. Buprenorphine stops withdrawal without causing intense euphoria.

Past a certain point, higher doses do not further intensify the pharmacological effects of buprenorphine but may increase the length of withdrawal suppression and opioid blockade. This is in contrast to full opioid agonists such as methadone and heroin, which exert greater opioid receptor activity as the dose is increased (see Figure 3). Nevertheless, buprenorphine can have strong opioid effects in non-opioid tolerant individuals.

Figure 3



Buprenorphine also has a high **affinity** for *mu* opioid receptors. This means that it binds very tightly to these receptors, preventing other opioids from attaching. This allows buprenorphine to block the effects of other opioids taken subsequent to buprenorphine. It also has slow **dissociation** (— letting go) from these receptors, allowing the clinical effects of buprenorphine to last significantly longer than would be expected based solely on its elimination half-life.

Buprenorphine is readily absorbed through the gastrointestinal and mucosal membranes. However, due to extensive first-pass metabolism, buprenorphine has very poor oral bioavailability (10 percent of the intravenous route) if swallowed. Its availability is significantly increased with sublingual administration (30-50 percent of the intravenous route) making this a feasible route of administration for the treatment of opioid dependence. Absorption of buprenorphine from the film preparation is greater than that seen with the tablets leading to a slightly higher peak concentration in the blood.

WHAT FORMS DOES IT COME IN?

Buprenorphine is administered sublingually and is available in three formulations:

- **Subutex** - contains only buprenorphine.
- **Buprenorphine** (generic)



- **Suboxone** – contains buprenorphine and naloxone



- **Suboxone Film-** contains buprenorphine and naloxone.



Naloxone is an opioid **antagonist** (blocker). It is used to discourage the non-medical, intravenous use of buprenorphine. It reduces the euphoria that buprenorphine produces if it is injected. The buprenorphine/naloxone combination is preferable in all cases except when the patient is hypersensitive to naloxone or pregnant. (Hypersensitivity may be demonstrated by rashes, hives, itchiness, bronchospasm, swelling and anaphylactic shock). Two other forms of buprenorphine, Buprenex, (a liquid, injectable form) and Butrans (a dermal patch) are not approved for use in the treatment of opioid addiction.

HOW IS BUPRENORPHINE METABOLIZED?

Buprenorphine is metabolized in the liver, primarily by the cytochrome P450 3A4 system, into norbuprenorphine and other products. Peak plasma concentrations are achieved 1-2 hours after sublingual administration. Peak clinical effects occur 1-4 hours after sublingual administration, with continued effects for up to 12 hours at low doses (2mg) but as long as 48-72 hours at higher doses (16-32mg).

Buprenorphine has a distribution half-life of 2-5 hours. The metabolites are excreted in the biliary system, with enterohepatic cycling of buprenorphine and its metabolites. Most of the drug is excreted in the feces and urine. Buprenorphine has an elimination half-life of 24-37 hours.

WITHDRAWAL SYNDROME FROM BUPRENORPHINE

Because buprenorphine is a partial opioid agonist and because it is slower to dissociate from opioid receptors than full opioid agonists, buprenorphine has a milder withdrawal syndrome when treatment is discontinued than that seen with full opioid agonists such as methadone. Typically, the withdrawal syndrome following abrupt cessation of long-term buprenorphine treatment emerges 2-5 days after the last dose and mild withdrawal features can continue for several weeks.

DRUG INTERACTIONS

The principal drug interactions of buprenorphine relate to its opioid activity.

- **Other sedatives-** Buprenorphine exerts additive CNS and respiratory depressant effects when used in conjunction with other sedating medications. These include benzodiazepines, alcohol, tricyclic antidepressants, and sedating antihistamines. **Deaths have been reported involving the combination of buprenorphine with high doses of benzodiazepines.**
- **Opioid antagonists-** Buprenorphine treatment should not be combined with opioid antagonists (naltrexone). Buprenorphine has a higher affinity for mu opioid receptors than the opioid antagonists. In the event of overdose of buprenorphine high doses of naloxone (10mg or more) may be required to reverse its effects. Naltrexone can precipitate a delayed withdrawal reaction in patients on buprenorphine.
- **Opioid agonists-** Buprenorphine exerts a degree of blockade to the effects of full agonist opioids which may complicate the use of additional opioids for analgesia. The initial dose of buprenorphine can precipitate opioid withdrawal in patients with high levels of physical dependence to full opioid agonists.
- **Hepatic enzyme inducers and inhibitors-** Buprenorphine is metabolized by the hepatic microsomal enzyme system (CYP 3A4). Theoretically, the use of foods or medications that inhibit the 3A4 enzyme (such as fluconazole, metronidazole, indinavir, ritonavir, erythromycin) may lead to increased plasma levels of buprenorphine whereas exposure to substances that induce the 3A4 system (such as phenobarbital, rifampin, phenytoin, carbamazepine, nevirapine) may lead to decreased levels of buprenorphine. Clinically, these medications have relatively minimal impact on buprenorphine-dosing requirements. Each patient should be managed on an individual basis.

BUPRENORPHINE SAFETY

Buprenorphine has a favorable safety profile. Because of the ceiling effect of mu opioid receptor activation (See Figure 3), respiratory and central nervous system depression is **significantly** less with buprenorphine as compared to full opioid agonists. In adults, overdoses on buprenorphine alone are almost never (if ever) fatal. However, it is possible for non-tolerant individuals to overdose on buprenorphine. Therefore, care should be taken in prescribing buprenorphine to individuals who are not fully tolerant to opioids. Fatalities have occurred primarily when buprenorphine was used intravenously along with intravenous benzodiazepines. It is important for a physician to be aware of the patient's concomitant use of other sedative hypnotics such as benzodiazepines. However, benzodiazepines and other CNS depressants, at therapeutic doses, can be used safely in combination with buprenorphine. If the use of benzodiazepines or other

CNS depressants is deemed medically appropriate, it is important to monitor closely for side effects, particularly sedation and respiratory depression.

DSM-IV-TR Diagnostic Criteria for Opioid Dependence:

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- Tolerance, as defined by either of the following:
 - A need for markedly increased amounts of the substance to achieve intoxication or desired effect, or
 - Markedly diminished effect with continued use of the same amount of the substance.

- Withdrawal, as manifested by either of the following:
 - The characteristic withdrawal syndrome for the substance, or
 - The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.

- The substance is often taken in larger amounts or over longer period than was intended.

- There is a persistent desire or unsuccessful efforts to cut down or control substance use.

- A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g. chain-smoking), or recover from its effects.

- Important social/occupational/recreational activities are given up/reduced because of substance use.

- The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Patients presenting with a clear history of opiate addiction but who are not currently physiologically dependent (such as patients recently released from a correctional facility or in-patient hospital or treatment center) may be at high risk for relapse and can be started on buprenorphine maintenance. However, in the absence of current physical dependence the

prescribing physician must clearly document potential benefits to the person's health and well-being that outweigh the potential disadvantages of buprenorphine treatment.

1. The patient must be able to give informed consent for buprenorphine treatment.
2. The patient must be able to adhere to the treatment plan. Treatment centers should carefully consider a patient's ability to attend counseling and medication dispensing sessions based on his/her work schedule, transportation, child care or other needs before accepting patients for treatment. As much as possible, treatment centers should be flexible in accommodating patients' needs.

RELATIVE CONTRAINDICATIONS

There are several medical conditions, as well as concurrent abuse of other drugs that may be relative contraindications to buprenorphine treatment.

- **Concomitant Acute Psychiatric Conditions** – Buprenorphine treatment should not be initiated in anyone with acute psychosis or other severe presenting psychiatric conditions which severely compromise the patient's ability to give informed consent for treatment.
- **Significant Current Pain** – The sublingual formulations of buprenorphine are not FDA- approved for the treatment of pain in the United States. Therefore, the BBI does not permit prescribing buprenorphine solely for treatment of pain. Patients with significant pain and opiate addiction must be evaluated on an individual basis. Some of these patients can achieve adequate pain control with buprenorphine (often dosed 2-4 times per day) along with other non-opioid medications such as NSAIDs. For patients with significant acute pain, it may be appropriate to transition them from opiates to buprenorphine as the acute pain improves.

PRECAUTIONS

Particular caution should be exercised when assessing the appropriateness of buprenorphine treatment for anyone with any of the following clinical conditions.

- **High-Risk Poly Substance Use** - The BBI recommends patients with poly drug dependencies be evaluated carefully to determine the other substances that are being used. Some patients who use other substances (see below) may not be appropriate for the BBI and/or may need an alternate level of care. Patients who occasionally drink alcohol can be started on buprenorphine.

- **Dependence on Benzodiazepines-** Buprenorphine has demonstrated synergistic sedative effects when used in combination with benzodiazepines. Deaths have been reported when buprenorphine has been used in combination with high doses of benzodiazepines. Therefore, the BBI does not generally advise programs to prescribe buprenorphine to people with significant current physical dependence on benzodiazepines. Patients presenting with a history or current use of benzodiazepines should be carefully evaluated to determine his/her pattern of use and potential for withdrawal. If the patient is currently physically dependent on benzodiazepines, he/she should be referred for detoxification and then re-evaluated as to whether he/she is appropriate for buprenorphine treatment. Patients with occasional illicit use of benzodiazepines or those taking prescribed benzodiazepines appropriately may be started on buprenorphine.
- **Alcohol Use-** Although there are no reports of death attributed solely to the combination of buprenorphine and alcohol, the potential for synergistic CNS and respiratory effects does exist. Patients with significant history of alcohol use should be evaluated carefully and referred for detoxification if necessary.
- **Severe Hepatic Impairment-** Physicians are to use their clinical judgment when prescribing buprenorphine to patients with significant hepatic impairment because buprenorphine is metabolized by the liver. The patient should be monitored closely (with liver function tests initially and every 3-6 months) if buprenorphine is prescribed. Simply being positive for hepatitis B or C does **not** indicate severe hepatic impairment.
- **Pregnancy-** Buprenorphine is classified as a Pregnancy Category C medication by the FDA (like methadone). Until recently, the recommended treatment for opiate dependent pregnant women was methadone maintenance. While methadone is still used, recent data from the Mother Study indicate that buprenorphine is safe and effective in pregnancy. The BBI recommends that any pregnant woman seeking treatment through the BBI receive a comprehensive assessment for appropriateness of buprenorphine vs. methadone. A BBI physician (Dr. Welsh or Dr. Olsen) can be contacted to discuss. Subutex should be used in these cases.
- **Breast Feeding-** There is limited literature available regarding the safety of buprenorphine by lactating women. Because of buprenorphine's poor oral bioavailability in infants, low levels found in breast milk, and low levels found in the serum and urine of breastfed infants, its use is acceptable in nursing mothers.

- **Other Medical Conditions-** Buprenorphine is an opioid and caution should be used in the following situations: (1) Recent head injury with the possibility of increased intracranial pressure and (2) Severely compromised respiratory function.
- **Non-tolerant Patients-** Patients who are not fully tolerant to opioids but who are at high risk of relapse and wish to begin treatment should be started at the lowest possible dose.
- **Transfer from Methadone Maintenance-** Buprenorphine may precipitate withdrawal in patients transferring from methadone. This is most likely to occur in patients on higher doses of methadone.