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Buprenorphine for the Management of Opioid Dependence

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Introduction:

Once again the United States is experiencing a major epidemic of opiate dependency. One hundred years ago physicians commonly prescribed morphine maintenance treatment. Their patients included Civil War veterans initially treated for pain and dysentery, and middle class women addicted to 'tonics'[1,2]. Regulatory restrictions imposed in the United States, notably the Harrison Act of 1914, prohibited opiate maintenance and ended the role of physicians in the treatment of opiate dependence[3]. Even after methadone was developed in the 1960's as an effective and safe oral maintenance medication[4], excessive regulation severely limited effective use. As a result less than 10% of the addicted population have received methadone, and only in heavily regulated clinics that are usually physically and functionally isolated from mainstream medical care. Today most physicians have little–to-no training or experience treating addictions[5], frequently failing to address them preventatively and belatedly offering limited treatment options in a manner that may fall short of standards expected for any other chronic medical disorder[6]. In 2002 the FDA approved sublingual formulations of buprenorphine [subutex and suboxone] and scheduled them to CIII, at last returning treatment of opioid dependence to standard office-based medical practice. This article will review the clinical use of buprenorphine for the treatment of opiate dependence and will help prepare physicians interested in incorporating this promising new treatment option into their practice.

Overview:

People abuse opiates to feel good or feel better. They relieve pain or provide rewarding euphoria through agonism at the mu-opioid receptor and indirectly through activation of the dopaminergic reward system in the nucleus accumbens. Opiates 'hijack' the reward systems of the brain. This signal, together with the qualititative context of use focus attentional bias on obtaining what is now considered most important. and determines the associations that will serve as future cues[7]. Tolerance develops immediately, but its extent depends on the amount of receptor activation, the potency of drug, route of administration, frequency and duration of exposure, and pharmacokinetics at the mu receptor. Drugs with shorter half-lives and binge-pattern use induces tolerance more rapidly. Once tolerance occurs the user will want to take increasing amounts of opiates to achieve the desired effect or stave off withdrawal. At this point opiates are taken to maintain an altered homeostatic set-point measurable in the hypothalamic-pituitary-adrenal axis, memory and hedonic pathways[8]. Patients feel miserable, stressed and apathetic without them and are sensitive to associated cues[9]. This state persists indefinitely as reflected in relapses many years after attaining hard-won or enforced sobriety. Buprenorphine can restore and normalize this dysfunctional state permitting patients to take renewed interest in other healthy reinforcers, such as love and work.

Epidemiology

Opiates have been abused for centuries, but contemporary economic and political turmoil and burgeoning international markets have contributed to an unprecedented production and sophisticated distribution system that is minimally impacted by interdiction. Afghanistan currently determines the size and development of world markets and the purity of street heroin continues to

rise indicating abundant supply. The incidence of opiate addiction has increased internationally but has remained relatively stable in the United States. Approximately 3.7 million Americans have used heroin at least once in their lifetime and there are around 1 million chronic users[10]. Mortality of untreated heroin abuse is estimated at 1-3% per year, 13-50 times the general population, with half of the deaths due to overdose[11].

In the United States both the choice of opiate and the type of user have changed. NSDUH estimate that 31.2 million Americans have abused narcotic pain killers[10]. The recent introduction of more potent and cheaper heroin has been associated with an increase in insufflation rather than injection as an initial entry point for the recreational use of heroin, attracting a broader experimenting population. Additionally, the last ten years saw an aggressive marketing of prescription opioids, especially OxyContin[12], with a 12-fold-increase in sales and explosion of addiction in areas where heroin had scarcely penetrated, such as the rural ghettos of Appalachia. Younger populations are now abusing opioids. Adolescent heroin use has more than doubled [to 1.6% of 8th, 10th and 12th graders] in the last 10 years placing these risk takers who are likely to move on to injection use, at high risk of contracting HCV and HIV. An estimated 9.3% - 18% of 12th graders have used Vicodin and 5% - 10% have abused OxyContin[13]. Only cannabis out ranks opiates as the most commonly abused drug in high school. 30% of high school students say that opiates are easy to get. There has been a corresponding doubling of opioid related deaths and emergency room visits between 1994 and 2001 and this trend continues to rise[14].

Assessment: Use, Abuse, Dependence and Addiction:

DSM-IV criteria for abuse imply that drug use has incurred some harmful consequences, e.g. failure to meet role obligations, physical harm, legal or interpersonal ramifications. Dependence

criteria include tolerance and withdrawal, representing the development of neuro-adaptation and alteration of homeostatic set-point. Behavioral manifestations are escalating intake over time or in amount, desire to cut down, or failure to do so, spending more time involved in obtaining, using or recovering from the drug, sacrifice of other previously important activities and continued use despite knowledge of harm. The addicted person is compelled to use despite their logical appreciation of the negative consequences. Craving is not always present or related to relapse. Dependence as defined by the DSM-IV criteria is necessary before prescription of buprenorphine in the United States. INSERT TABLE 1 ABOUT HERE: DSM-IV CRITERIA FOR OPIOID DEPENDENCE. Screening tools can be useful, such as UNCOPE as below.

ADD TABLE 2 APPROX HERE

Accurate diagnosis must precede treatment. It would be tragic to expose the non-addicted brain to long term high potency opioid agonists such as methadone or buprenorphine. Conversely, treating the tolerant [neuro-adapted] brain with these agents cannot make someone into an addict.

Preliminary Goals:

After a discussion about confidentiality, the physician's approach to the addicted patient should be curious, inviting and thorough. The discussion should minimize shame and defensiveness. Over-familiarity and slang are not needed: patients appreciate that they are seeing a professional. The tone should be accepting and assumptive of extensive drug use and common aberrant behaviors. The aim is acquisition of data to help understand treatment options, rather than to provide an anticipated moralistic lecture.

Patients have personal values, objectives and priorities. It is important to dig a little deeper than the patients initial stated aims, to find out what they truly want and what they are reluctant to

give up. It is important to acknowledge their ambivalence. They recall benefits of drug use that the therapist must help them grieve or satiate in other ways. For example, the patient might need help appreciating that opioid use has not been fun, cool or stress-relieving for many years; or have anxiety or insomnia that needs treatment. Such "motivational nterviewing" skills can be easily learned and have significant impact on outcomes[15]. Questions about family and personal history of addictions and impulsiveness, and detailing the user's pattern of drug use provide very useful information. They provide an appreciation of the neurobiology of the patient: how novelty-seeking they are, how likely are they to resist cues, how vulnerable to stress, how prone to the rapid development of tolerance. Questions about mood and behavior in sober periods and before drug use began helps estimate how much self-medication might have occurred in the choice of drug. It is important to recognize that most people with addictions remember their histories as more disturbed than they really were, and most will feel that they are self-medicating by the time they come for treatment, given the effects of opiates on all aspects of their lives from the social level to the neuroendocrine level. Interviews with relatives may provide a more accurate history regarding early periods of use and can be indispensable in treatment. Sharing your treatment philosophy can be very helpful, clarifying discrepant goals and inviting optimistic collaboration. The majority of opioid dependent patients have other addictions, as well as co-morbid psychiatric or medical disorders that will have a major impact on retention and the success of treatment. Good data is 15-25 years old: the National Comorbidity Survey found that up to 66% of addicts have one or more psychiatric diagnoses in their lifetime[16] and the Epidemiological Catchment Area Survey[17] found that 42.7 % and 61% of schizophrenic and bipolar patients respectively have a substance abuse disorder. Studies suggest affective disorder is present in between 55% and 74% of opiate dependent patients[18,21]. 80% of methadone maintained patients have HCV

and/or HIV[19], half have chronic severe pain[20]. Assessment and treatment are essential. Psychiatric care should be integrated into the addiction treatment plan and should be provided together rather than trying to contain one [eg the addiction] before addressing the other.

Treatment: Non-pharmacological aspects of treatment:

Buprenorphine can normalize the dysfunctional, physiological state of dependence, permitting patients to take renewed interest in other, healthier, reinforcers. However, the patient must be able to identify and work towards realizing these other goals to make them salient and able to compete with the attractiveness of drug use. Treatment success depends on a therapeutic alliance and a contract entered into honestly. Goals must be realistic. If the physician expects only abstinence or psychological maturity, then disappointment is inevitable. Similarly, if the patient puts the physician in an impossible or unethical position, the contract needs amending. Flexibility is required as patients move erratically towards recovery. This process requires the physician to understand and be comfortable with the boundaries of safety and legality. Doctors considering treating opiate addiction should consider the size and scope of their practice. Physicians must be able to either provide appropriate counseling or have close ties to skilled addictions therapists and other necessary specialists and they must also be able to obtain urine and blood samples. Inevitably, some patients are too complex for office-based treatment and they should be referred to a more appropriate level of care. The following table helps consider the level of complexity of a specific patient. It is clinically, rather than research, based: TABLE 3 HERE

Pharmacological Treatment Options for Opioid Dependence.

Naltrexone, an antagonist at mu-opioid receptors, can be useful but compliance is generally poor, and side effects [including dysphoria and anxiety] may be severe in some patients. Clinically, it is only used with highly motivated patients, or individuals who cannot, or will not, use agonists. Methadone is a pure mu-opioid agonist that can be administered once daily. Forty years of experience and research have confirmed that at doses of 80-120mg/day it can eliminate use, craving and withdrawal and block the ability to get euphoric from additional opiate abuse**Error! Bookmark not defined.**. Importantly, it normalizes brain and endocrine physiology disrupted by the cyclic administration of a short-acting agonist [eg heroin], in particular abnormalities of the hypothalamic-pituitary-adrenal axis. When administered in a well-run treatment program, this drug has profound personal and public health benefits including a drastic reduction in transmission and acquisition of HIV and HCV, incarceration and mortality. It is safe and cost-effective but less than 10% of heroin-dependent addicts in the United States receive maintenance treatment. There are only 200,000 treatment slots nationally, in highly regulated clinics where treatment is sometimes poorly delivered, with the consequent perception of treatment failure[22]. Methadone has typical opioid side-effects and several clinically important drug-drug interactions. It can be administered in pregnancy and to lactating mothers, and in patients with severe liver or renal failure. The main draw-back of methadone is its stigma and regulatory restrictions to prescription in office-based practice. Unfortunately, many patients also receive substandard treatment. For example, in 2002 the average maintenance dose was only 47 mg/d[23], a dose that is well below recommended levels and is often associated with disappointing results. Nonetheless, methadone represents the gold standard in addictions treatment. LAAM [levo-alpha-acetyl-methadol] is a long acting form of methadone that permits thrice-weekly dosing. Following several deaths from

Torsade de Pointes, LAAM received a black box warning from the FDA and production was subsequently halted due to limited market demand.

Buprenorphine is a partial agonist at the mu-opioid receptor. It has many properties in common with methadone, making it a similarly good choice as an opiate replacement therapy. It is derived from the opium poppy, via the thebaine alkaloid. It has poor oral bioavailability, due to extensive GI and hepatic metabolism, and thus requires an alternative route of administration. There are parenteral and sublingual, and soon transcutaneous, formulations; depot formulations are also under development. Sublingual absorption of a tablet form permits the lipophillic parent compound to penetrate the CNS where it binds with high affinity to opioid receptors. Partial agonism means that receptor binding does not cause full activity: Effects plateau before they are full. Buprenorphine reaches a plateau at around 24mg. Clinically, this limits toxicity and the risk of overdose. Opioid-naive subjects [in a controlled setting] do not experience significant respiratory depression[26]. However, as buprenorphine is 30-times as potent as morphine as an analgesic it can be lethal when combined with sedatives-hypnotics [up to 2/3 opioid dependent patients have abused benzodiazepines in the past 6 months]. The limited agonism confers a less severe withdrawal syndrome when the drug is rapidly stopped, as compared to methadone or heroin[24].

Despite partial agonism, buprenorphine binds with high affinity and will displace most full agonists from the mu-opioid receptor. Buprenorphine binding to mu-opioid receptors in a naive subject will generate analgesia and mild euphoria. The same agent can feel like an antagonist in an opiate dependent individual if a full agonist is displaced from the receptor. This means that withdrawal is precipitated if buprenorphine is given too soon after an agonist has been used. It is difficult to displace buprenorphine with other opiates. This includes not only heroin, methadone,

oxycodone, etc, but also antagonists such as naloxone, so that overdoses are difficult to treat. Because buprenorphine dissociates very slowly from the receptor, it can be administered every few days despite more rapid metabolism in the periphery[25]. Once the drug dissociates it is deaklylated, primarily via cytochrome P450 3A4, to the active metabolite nor-buprenorphine. Norbuprenorphine is then glucorinated before excretion via the feces and kidneys.

Buprenorphine suppresses heroin self-administration in a dose-dependent manner, in both laboratory[26] and clinical setting. A large, multi-center randomized double-blind placebo-controlled study of sublingual buprenorphine demonstrated significant reduction of craving and use at both 8mg and 16mg doses[27].

Administration of the US product. Diversion issues, Naloxone, Suboxone.

In the United States the tablet form of buprenorphine comes as 2mg or 8mg [subutex, the "mono" formulation] or in combination with naloxone in a ratio of 4:1 [suboxone, the "combo" formulation]. The tablet is completely dissolved under the tongue over five minutes. It is important to coach patients on this, and discourage crushing to a paste, so that the drug does not undergo first-pass metabolism in the gut. Buprenorphine is not detected in routine urine toxicology, which is designed to detect morphine -derivatives. Clinicians can order a specific screening test for buprenorphine. The naloxone in the combo tablet may or may not show as low level opiate.

Naloxone is a pure antagonist but has poor oral bioavailability and sublingual absorption so that it passes largely unabsorbed into the feces, perhaps limiting constipation. The small amounts that enter the blood rarely cause any withdrawal symptoms, unless the patient is using a pure ag-

onist. If the patient attempts to inject the combo formulation, the concentration of naloxone might be high enough to cause precipitated withdrawal, discouraging further abuse. Such precipitated withdrawal would not occur if abusers are not dependent on pure mu-opioid agonsits or are only using and abusing suboxone or subutex. Such individuals will experience more intense euphoria. There has been little research to determine if the combination drug does indeed reduce abuse and there have been few studies testing if the combination drug is as effective as buprenorphine alone[28]. Nonetheless, both patients and clinicians have reported a high level of satisfaction with the combo formulation. Buprenorphine has a slow onset of action, making it less desirable to individuals seeking opiate intoxication. Diversion probably continues for several reasons: (1) the continued shortage of treatment (2) constraints on such treatment for those not prepared to endure them (3) self-initiated "treatment" by individuals wishing to avoid further use of heroin or other illicit opiates, but unwilling or unable to enter legitimate treatment (4) as a replacement for street heroin (ie for illicit purposes) (5) to sell (6) to store for a rainy day.

Buprenorphine Detoxification: Efficacy

Controlled opiate withdrawal, or detoxification treatment, generally has poor outcomes. Detoxification methods might involve use of an opioid taper or non-narcotic comfort medications including alpha-adrenergic blockade (clonidine). Ultra-rapid detoxification involves injecting an opioid antagonist under general anesthesia. The long-term efficacy of all studied detoxification is dismal, with relapse rates around 90%[29]. Ultra-rapid methods are additionally dangerous. Kakko et al[30] performed a small placebo-controlled trial of sublingual buprenorphine 16mg. Subjects were excluded if they were dependent on other classes of drugs. The placebo group received a 6-day buprenorphine taper followed by placebo plus high intensity and state-of-the-art

individual and group therapies. 75% of the maintained group remained in treatment for the year, whereas all placebo patients dropped out of the study and relapsed within 2 months. Mortality reached 20% in the buprenorphine taper/psychosocial treatment-only group, while none of those maintained on buprenorphine died. This study mirrors the results of a study of methadone detoxification vs maintenance[31] . Thus, the dependent patient is likely to relapse after completing either a slow taper or a rapid taper. Maintenance should be the rule rather than the exception.

Buprenorphine detoxification: Method

If detoxification is requested even after relapse rates are reviewed with the patient, then a buprenorphine taper can be initiated. Buprenorphine detoxification produces less severe withdrawal symptoms than does either methadone or a clonidine-assisted withdrawal protocol. Numerous protocols are available, ranging from 3 days to 6 months. There is little data to help choose between different protocols although there would be more of a chance to motivate, educate and support the patient's abstinence during a more prolonged detoxification. Detoxification protocols generally stabilize patients at 8-12mg and then taper by a percentage over the desired time period. As buprenorphine is long-acting, it will self-taper thereafter. The reader is referred to SAMSHA TIP 40[32].

Buprenorphine Maintenance: Efficacy

Most research studies of buprenorphine maintenance have been carried out in methadone clinics. These studies have demonstrated that buprenorphine is more effective than placebo, and equally effective as moderate doses of methadone and LAAM on the primary outcomes of treatment retention, illicit opiate use and craving[33]. Comparable results have been demonstrated in those tri-

als carried out in office-based settings. Amato, et al. has recently summarized the five Cochrane studies on substitution maintenance treatments[34]. These studies confirm that buprenorphine retains patients more than placebo and slightly less than methadone and that it decreases opiate use, again slightly less than methadone. In a series of studies, Strain[35,36] showed comparable efficacy between flexibly dosed sublingual buprenorphine [mean 9mg] as compared to low-dose methadone [mean 54mg] over 4 months. As could be anticipated from previous studies with methadone, almost all patients relapsed on discontinuation of maintenance treatment. In an elegant 17 week study (double-blind, flexible dosing, rescue procedure, control condition) Johnson[Error! Bookmark not defined.] showed that high dose buprenorphine [16-32mg thrice weekly] was equivalent to 'high dose' methadone [60-100mg] and LAAM [75-115mg/d equivalent] on measures of treatment retention [58%, 73%, 53% respectively], and reduced opiate use [as measured by reported use or the incidence of positive urine toxicology tests per week]. Cocaine use was also substantially reduced as typically occurs when opiate use is curtailed.

Both buprenorphine and methadone are excellent choices for opioid dependent patients. The most important difference is probably the regulatory restrictions on prescribing methadone. Clinical experience suggests that buprenorphine will be most effective with highly motivated individuals with smaller opiate habits. Methadone administered in the methadone clinic setting is the preferred treatment for individuals with larger habits, lower levels of motivation and more complicated psychiatric and drug use histories. Comparison studies lack the nuance apparent in clinical practice: some patients will do better on one drug than the other. Cardiologists have more than one antihypertensive drug for similar reasons.

Buprenorphine Maintenance: Method

Induction has three goals: elimination of withdrawal symptoms, elimination of cravings, and blockade of opioid induced euphoria, thus eliminating further opioid use. The rate of induction should be fast enough to maximize retention and slow enough to minimize side effects and diversion risk.

Induction should not begin until the patient is in mild to moderate withdrawal [assessed with tools like the OOWS or the COWS] indicating opiate dependence and reducing the risk of precipitated withdrawal. Physicians should educate the patient on how to let the pill dissolve sublingually for 5 minutes in the moist mouth. The risk of precipitated withdrawal should be explained before buprenorphine is administered. The initial dose range is 2-6 mg, depending of the patient's tolerance. The patient should remain in the office for 2 hours to ascertain reaction and fitness to leave the office [e.g. level of sedation]. If withdrawal worsens after the initial dose, most physicians continue with a second dose to achieve greater receptor occupancy rather than temporarily terminating the initiation process and risk losing the patient. The patient should be told to anticipate some cravings the first night of treatment and should be encouraged to resist additional illicit opiate use so as to permit increased dosing the following day. Most physicians use the combination formulation suboxone for induction as well as maintenance. On day 2, the patient should be asked what drugs they used the previous night, and how many hours they slept, indicating either sedation or increased withdrawal. Dosages can then be decreased, or more often, increased as necessary to a maximum of 16mg for the second day. Target doses for maintenance are usually 12-16mg a day.

If the patient is being transferred from methadone treatment to buprenorphine, the methadone dose should be tapered to 30mg a day and maintained for at least 7 days. The patient should then

skip one day of methadone and then initiate buprenorphine as soon as early withdrawal symptoms can be documented. Because of the patient's higher level of tolerance, the final buprenorphine dose may be as high as 32mg.

If the patient is not currently dependent on opioids but is at high risk for relapse, e.g. a previously dependent person on release from jail or hospital, or a previously maintained patient who has resumed occasional illicit use, buprenorphine can be initiated at 2mg and increased by 2mg each day until the patient is stabilized.

Prescriptions should not be given until induction is complete, and should initially be for small quantities. Random call-backs should occur to check compliance and to prevent diversion. Most patients will need daily dosing, although research protocols have shown that many patients can be managed on as few as three doses a week at up to 32mg each dose**Error! Bookmark not defined.**. This dosing approach is not recommended except in methadone clinics where buprenorphine take-home doses are limited by federal regulations. Contrary to expected pharmacokinetics, a few patients complain that they need to take a dose twice a day to obtain relief of craving. At times, the authors have provided such prescriptions on a case-by-case basis.

Length of Treatment:

There is little data to guide clinical decisions regarding the optimal length of buprenorphine treatment. Clinicians can extrapolate from extensive research with methadone and from the Kakko study cited above. With methadone, even carefully selected patients with good prognostic factors usually relapse when tapered. As patients presenting for buprenorphine treatment tend to be younger and have shorter addiction histories, some physicians are reluctant to prescribe opioid maintenance. However, these patients are still opioid dependent and the argument could

be made that their impulsiveness[37] and peer groups make recovery more challenging. Most experienced clinicians recommend long-term treatment. Motives for voluntary taper should be explored as this frequently uncovers issues in the patient's life or relationships that need attention. We advise discontinuation only when someone is more prepared to weather cravings, insomnia, mood shifts and impulsiveness than previously. Referring back to Figure 1, such a patient might have shifted to have more qualities from column 2. Peer support groups should be an active part of the treatment plan and the patient should be engaged in effective counseling. The patient must be warned that any future exposure to stress or opiates could trigger a relapse. A buprenorphine taper cannot be done too slowly.

Who Can Prescribe and How?

In the United States, suboxone and subutex products were scheduled into C III of the Controlled Substances Act. Any physician can prescribe these drugs for pain, but physicians wishing to prescribe for the treatment of opiate dependence must apply for a waiver from SAMHSA and show that they have received sufficient training, at minimum 8 hours at a certified course, or that they have their addiction psychiatry boards or have been certified by American Society of Addicion Medicine. To date, over 5000 physicians have received waivers. Physicians can treat up to 30 patients each, and a recent amendment to the Controlled Substance Act [2005] eliminated the limit on the number of patients that can be treated in a group practice. Physicians should initiate random medication call-backs to detect diversion and drug abuse. Some physicians keep a supply of medications in their offices so that they can avoid giving a prescription to new patients of undetermined reliability, who might not return for further treatment. If buprenorphine is

locked in the physician's office, there must be careful security and documentation that complies with state and DEA requirements.

It is important to be straightforward with the patient regarding anticipated limitations of treatment. It is best to spell out in detail what the patient can expect from the physician and what the physician expects from the patient in terms of appropriate behavior and compliance with treatment. Contracts are a useful way of addressing and documenting these concerns. It is important that the physician honor the contract, even if discharge or referral to a higher level of care is required. If contract violations indicate that the risks of treatment outweigh the benefits, the physician who refers a patient to a more intense level of treatment is not abandoning the patient. Office-based care is not appropriate or effective for patients with extreme behavioral problems. Table 4 lists common elements that should be addressed in the treatment contract.

TABLE 4 APPROX HERE

Buprenorphine Safety:

Buprenorphine is a highly potent but relatively safe medication. Toxic effects are limited by poor bioavailability [limiting levels obtained after accidental oral ingestion], partial agonism and slowed onset of action. Side effects are those typical of mu-opioid agonists. Euphoria and sedation will occur if buprenorphine is ingested by anyone who is not tolerant to opiates. Respiratory depression has not been a problem with buprenorphine, unless the drug is taken in combination with alcohol or another sedatives. A number of deaths were reported in France, associated with the injection of illicit buprenorphine in combination with high potency benzodiazepines[38]. Antagonist reversal of a buprenorphine overdose is difficult because buprenorphine binds to the re-

ceptor more tightly than naloxone, and has additional kappa-opioid receptor effects that might be pertinent.

Less problematic side effects are nausea, constipation, sweating, sexual dysfunction, bitter taste of the pill, and dry mouth. This latter, combined with the addict's proclivity to sweet foods and poor dental hygiene can cause severe oral caries. There is no evidence of impaired response time or other cognitive disturbances limiting driving. Patients should be informed that buprenorphine maintenance will interfere with the use of opiates for the treatment of acute or chronic pain [see below].

Pharmacodynamic drug interactions alter effects of a drug at the target organ. An example of this occurs when abused benzodiazepines or neuroleptics increase the risk of respiratory depression. Pharmacokinetic interactions occur when a co-adminstered drugs alters the absorption, distribution, metabolism or excretion of buprenorphine. Metabolism of buprenorphine is chiefly at the cytochrome p450 3A4 site. Strong inhibitors at this site may reduce buprenorphine levels. They include macrolides, antifungals such as ketoconazole, and protease inhibitors such as ritonavir. Inducers include antiepileptics [phenobarbital, carbamazepine, phenytoin], rifampicin and efavirenz. Oral contraceptives are commonly metabolized at this site too. There have been few studies of these specific drug-drug interactions, but it is possible that the high affinity that buprenorphine has at the mu-opioid receptor makes variations in blood levels less relevant. For example, efavirenz does not cause opiate withdrawal in buprenorphine maintained patients[39]. To date there have been no clinically relevant interactions reported. Therefore, clinicians should be vigilant for actual rather than predicted effects and modest dose adjustments should generally resolve most of these interactions.

Treatment of Special Populations.

Clinical trials with buprenorphine have found no significant organ damage associated with chronic dosing. Buprenorphine is minimally excreted via the kidneys so that renal failure is not pertinent. However, buprenorphine may be associated with increases in liver function tests; this may be especially true for patients with a history of hepatitis prior to the onset of buprenorphine treatment.

Up to 50% of injection drug users have serological evidence of prior exposure to Hepatitis B, 2-10% of which progress to chronic hepatitis. Hepatitis C is far more contagious and prior infection is evident in 90% of injection drug users, 20% of whom will develop cirrhosis over 20 years, making HCV the leading cause of liver transplant. Treatment is available but arduous. Ongoing drug abuse is associated with poor treatment compliance and worsening mood, and usually precludes effective treatment. Buprenorphine-induced elevations in liver function tests (LFTs) appear to be mild. It is important to keep in mind that other factors commonly found in opioid-dependent patients (such as hepatitis and alcohol abuse) can lead to elevations in LFTs. Such transient elevations in LFTs are very common in this population. Most patients with complex medical problems do better if their addiction is stabilized with a daily medication. If LFTs do increase, the patient can be switched to methadone, with an established absence of hepatotoxity.

HIV affects 15-20% of injection drug users. Treatment involves the use of multiple medications with potential for cytochrome interactions. Buprenorphine does not seem to have any major short-term impact on HIV viral load measurements following treatment with HAART, and it is possible that buprenorphine poses less complicated drug interactions than does methadone. Tuberculosis is another common disorder in addicted populations and requires careful monitoring for medication interactions in buprenorphine patients, although none have yet been described.

Available data about the use of buprenorphine in pregnant, opioid-dependent women has been primarily limited to case reports. Opioid replacement therapy in pregnancy minimizes risk of exposure to infections through ongoing intravenous drug use and premature labor induced by withdrawal. Methadone has a proven efficacy and safety record, and comparable data has been slowly accumulating for buprenorphine[40]. There have not been any reports of significant problems attributed to buprenorphine use during pregnancy and early data suggest that the neonatal abstinence syndrome might be milder than in methadone-exposed infants. Many hospitals have specialized services for this high-risk group. The mono buprenorphine product [subutex] is prescribed during pregnancy because naloxone's teratogenicity is unknown. There is little data on lactation, but less than 10% of the drug is passed into the breast milk and then the bioavailabilty is very low. Thus, the benefits of breast feeding likely outweigh the risks.

Adolescents are the fastest growing opioid-dependent group. Even more than for adults, there is a reluctance to start opiate replacement therapy in adolescents because of the concern about exposing the developing brain to long-term and steady-state opioids. Conversely the developmental changes in neurocircuitry seen in adolescence might contribute significant vulnerability to addiction and justify earlier agonist replacement therapy[41]. There is only one clinic in the United States for methadone maintenance for adolescents [the Adolescent Methadone Program at the New York Presbyterian Hospital]. Many states prohibit such treatment. However, given the high rate of failure for abstinence-based treatment and the concern that adolescents are more likely to use and share needles, the physician must carefully weigh the risks and benefits of any treatment option. Concern about the acquisition and dissemination of HIV or HCV, as well as the social and psychological harm associated with relapse and ongoing opiate abuse makes bu-

prenorphine treatment an attractive alternative for adolescents. Detoxification should be attempted at least once before recommending maintenance for the adolescent. There is only one detoxification protocol [without follow-up data beyond the six month trial] showing the safety and utility of buprenorphine for adolescents[42].

Acute pain can be treated with opioids in the opioid dependent patient when indicated. Many opioid dependent patients have lowered pain thresholds. Even though a single dose of buprenorphine eliminates cravings and withdrawal for 24-hours, its analgesic action is only 6-10 hours. Sometimes a switch to dosing three times a day [at higher total dose] is sufficient to control acute pain. Another approach is to dispense higher or more frequent doses of another opiate to override the antagonist properties of buprenorphine. Otherwise buprenorphine can be discontinued while a stronger agonist, for example methadone, is used. Once the acute episode has passed the patient can resume buprenorphine following principles outlined in the Buprenorphine Maintenance: Methods section above.

Many opioid dependent patients have chronic severe pain [up to 60% in some methadone clinics**Error! Bookmark not defined.**], because of injury, or altered pain perception and tolerance. If this requires opioid management then buprenorphine can be divided into three times a day dosing although the FDA has not included pain as an indication for the sublingual formulation. Sometimes a pure agonist will be necessary and a switch to methadone is an appropriate alternative. Experience in this arena is accumulating.

Conclusions:

Addictions make everyone uncomfortable. People who suffer from an addiction often feel great shame. Family and society often turn a blind eye before becoming angry with the sufferer. Regulations historically reflected this ambivalence and stymied treatment throughout the twentieth century. Assessment and treatment are often provided by

abstinence-oriented clinicians who are inadequately educated on evidence-based practices. Given that addictions are so common and so frequently impact compliance and management of other conditions, the medical establishment has been failing their patients and their public health responsibilities. Physicians are also missing out: there are few opportunities in psychiatry when one can save life, relieve profound suffering and assist deep transformation. In the forty years following the development of methadone maintenance programs, a few physicians have enjoyed the privilege of doing this work. Now, with the introduction of buprenorphine into mainstream practice, physicians can address addictions with respectful thoroughness and practice this highly effective, and deeply rewarding intervention.