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MEDICAL TREATMENT: Barriers to implementation of buprenorphine in opioid addiction treatment.[1]

SUMMARY

Buprenorphine, a partial agonist and partial antagonist to opioids, has recently been approved for use by physicians, in an office practice, in slow detoxification and harm reduction for opioid dependent clients. Although there is a significant need for a new modality in treatment of opioid dependency, in California the response by physicians has not been enthusiastic. In six Northern California counties issues of perceived need, cost-effectiveness, resistance by established medical centers and methadone clinics may have constituted barriers, initial indications are that physician attitudes are the leading obstacle to rapid implementation of the treatment modality.

ARTICLE

Certification of Subutex and Suboxone for Opioid Treatment

Buprenorphine, a derivative of Thebaine, under the proprietary formulations Subutex and Suboxone, was certified by the United States Food and Drug Administration (FDA) on October 8, 2002, for the treatment of opioid addiction in physician's offices on an outpatient basis. The manufacturer, Reckitt Benckiser Pharmaceuticals, received FDA approval to market the Buprenorphine monotherapy product, Subutex, and a buprenorphine/naloxone combination product, Suboxone, for use in opioid addiction detoxification and opioid substitution treatment. In January 2003, Reckitt Benckiser began shipments of Suboxone® to pharmacies in the United States. It is the first narcotic drug for the treatment of opioid dependence that may be provided in a physician's office-as allowed under the Drug Addiction Treatment Act of 2000 (DATA 2000), rather than through special treatment facilities, as is the case with methadone.

To be certified to dispense Subutex and Suboxone, under Title 42 Code of Federal Regulations Part 8 (42 CFR Part 8), physicians need only file for waiver from the requirements of Section 304 of the Controlled Substances Act (21 U.S.C. 824) by identifying themselves by name, address, phone number, a Drug Enforcement Administration (DEA) number and requesting certification to dispense the drugs through the Substance Abuse And Mental Health Services Administration (SAMSHA), using SAMSHA Form 167 (SAMSHA, 2003a). The form requires the physician to provide proof of completion of eight hours training in the administration of the drugs, or be certified as an addictions specialist in psychiatry, addictions medicine, osteopathy, or any other recognized medical board specialization in addictions, or having participated in one of the field trials leading to approval of the drugs, or otherwise demonstrate competence in the treatment of opioid dependence. The physician must promise to treat no

more than 30 addicts at any given time, and must agree to refer the patients for full-spectrum care for the social and psychiatric issues associated with drug dependency. The certification process was initiated in 2002, when SAMSHA began professional training in the use of the drugs.

Despite the relative ease of qualification, only 130 California physicians have been certified by the DEA and SAMSHA to dispense the drugs, including 1 in Stockton, California, and none have been certified in Stanislaus, Amador, Calaveras, Mariposa, or Tuolumne Counties, as of April 4, 2003 (SAMSHA, 2003b). This paper will address the scope of need for Buprenorphine treatment, its place in the spectrum of treatment options available, and perceived barriers to implementation of the treatment option in the selected California counties.

Scope of Need For Treatment

In 1999 there were 179,000 treatment admissions for primary injection drug abuse and 34,000 admissions for secondary injection drug abuse (DASIS, 2001). Opiates accounted for 83 % of admissions for injection drug abuse, followed by methamphetamine/amphetamine (11 %) and cocaine (5 %). According to the 2002 National Drug Threat Assessment (USDOJ, 2002), opioid use in the United States has been increasing steadily since the early 1990s. No longer confined to the urban areas of the country, heroin use occurs in rural and suburban areas as well. Older users, those over 35, continue to be the largest user group. Suburban consumers aged 12-25 have been one of the fastest growing user groups in the 1990s, according to the assessment. Prevalence is highest among whites followed by Hispanics and African Americans. Users are predominantly male, but use among females has increased.

New users often begin by smoking, sniffing, or snorting the drug instead of injecting it. Heroin's reasonably low price and high quality enable users to snort or smoke the drug, removing the stigma and risk associated with injection. Many new users and young people mistakenly believe snorting or smoking the drug will not lead to addiction.

The introduction of high purity Heroin (diacetylmorphine) to the market in the early 1990s may account for the increase in Heroin use. Other factors include introduction of a fentanyl analog with over 100 times the analgesic strength of morphine in 1996, and increases in abuse of oxicodone and methadone. The higher purity enables users to effectively snort, sniff, or smoke opioids, removing psychological barriers to and the stigma of intravenous drug use. The Threat Assessment reports that the proportion of lifetime opioid users who had ever smoked, sniffed, or snorted opioids increased from 55 % in 1994 to 71 % in 1997.

The White House (U.S. Office of National Drug Control Strategy, 2003) estimated that by 2001, over 3,019,100 Americans had abused opioids, during their lives. Opioid addiction affects between 810,000 (Fiellin, Rosenheck, Kosten, 2001; Woody, Juday, Kleber, 2001), and 898,000 (2001 estimate, U.S. Office of National Drug Control Strategy, 2003) persons each year, with approximately 180,000 in treatment at any given time (NIDA, 2002a). The California Department of Alcohol and Drug Programs (ADP, *Household Drug Summary*, 1999) estimate through 1999, was that 3.9%, or 1,345,500, of all Californians had abused opioids, lifetime, and .03 %, or 153,000 Californians, are addicted at any given time. If, as postulated by NIDA (NIDA, 2003), only one in five opioid addicts are in treatment at any one time, approximately 31,000 Californians are obtaining treatment for opioid dependence. As of April 3, 2003, the California Department of Alcohol and Drug Programs has licensed treatment facilities statewide to treat 41,336 opioid dependent clients (ADP, 3003).

Opioid abusers frequently use their drug of choice, Heroin, fentanyl or its estimated 15 analogs, morphine or an estimated 38 analogs, oxicodone, methadone, hydrocodone, meperidine, or hydromorphodone, in conjunction with other drugs, particularly cocaine and alcohol (Epstein, Gifroerer, 2003). Among persons admitted to emergency rooms for opioid overdoses, 54% were admitted for opioids in combination other drugs, including cocaine in 28%

of admissions, and alcohol in 27% of admissions. Another study, of 581 opioid users tracked in California's Civil Addict program from 1964 through 1997, indicates 66.9 % were also addicted to tobacco, 40.5 % continued to use opioids, 33.55 % used cannabis, 22.1 % were heavy alcohol users, 19.4 % used cocaine, 11.6 % used amphetamines, and 10.3 % used crack cocaine (Hser, et al, 2001). An earlier study identified 50-75% of male opioid abusers and 25-50% of female abusers, were also addicted to alcohol, and over half of all opioid abusers also abuse sedative-hypnotics, particularly benzodiazapines (Belkin, Gold, 1991).

A 1981 survey indicated that once opioid dependence develops, 25 % of opioid addicts die within 1-20 years of active use, usually as the result of suicide, homicide, accidents, and infectious diseases (O'Brien, Woody, 1981). The 33-year study conducted by Hser, et al, reported 48.9 % of the original sample had died during the study, 21.6 % from drug overdose, 19.5 % by homicide/suicide/ accident, 15.2 % from chronic liver disease, 11.7 % from cancer, 11.7 % from cardiovascular disease, and 3 (.05 %) from Acquired Immunodeficiency Syndrome (AIDS). Treatment effectiveness was not a focus of the study, although the investigators remarked that their prior findings (Hser, et al, 1995) indicated methadone maintenance treatment did reduce opioid use among the group, and the high relapse and continued opioid use among the group was related to less than 10 % of the sample group participating in treatment at any one time.

Traditionally, the most serious consequences of opioid abuse occur when the drug is injected. Risk factors include HIV and hepatitis transmission, site infection, and greater potential for fatal overdose due to rapid transmission of the drug to the central nervous system. In California, according to the California Drug Threat Assessment (USDOJ, 2001b), additional dangers occur when mixing opioids and cocaine as an injected "speedball" and from the practice of dissolving black-tar Heroin with citric acid, resulting in ulcerations and exotic site infections. Indicators suggest that many of the newer opioid users are snorting and, to a far lesser extent, smoking the drug, believing these methods will not lead to addiction. In some areas, "shabanging", picking up dissolved opioids with a syringe and squirting it up the nose, has increased in popularity among younger users. In the Northwest, "cross-lining", snorting alternate lines of opioids and cocaine is developing in popularity, but is not yet believed to have caught on in California. Unfortunately, as an addiction develops tolerance level increases, and users will often switch to injection, a more efficient method to administer the heroin. The smaller doses required for injection also cost less, making injection financially attractive to frequent users.

While many opioid users start out gainfully employed, the overwhelming need to support their habits often leads to criminal behavior such as prostitution, drug dealing, and robbery. Opioid use is not normally associated with violence; however, opioid abusers may commit crimes such as robbery and burglary to support their drug habits. Heroin trafficking, like the trafficking of other drugs, is accompanied by criminal activity. Criminal groups and individuals involved in the trafficking and distribution of the drug may use violence to protect drug shipments or to maintain control over distribution in a given area.

Street gangs, many of which are known to commit violent acts, are involved in the distribution of drugs throughout California. The DOJ threat assessment summaries estimate that street gangs distribute 20 % to 50 % of the drugs in their areas. These gangs are also involved in drive-by shooting, homicide, carjacking, and home invasion crimes, most of which are not classified as drug-related.

Another measure of the relationship between criminal behavior and drug use is the percentage of arrestees testing positive for drugs, in this case opiates. According to the USDOJ California summaries, opioid use among adult male arrestees in California increased slightly between 1995 and 1998. In 1995, 8 % of male arrestees tested positive for opiate use while 9 % tested positive in 1999, a 1 % increase. Comparatively, the percentage of female arrestees

testing positive for opioid use decreased from 12 % in 1995 to 10.9 % in 1999, a 1 % decrease. Opioid use among male juvenile offenders (ages 9 through 18), decreased slightly during the same time frame, from 1 % in 1995 to .4 % in 1999. The summaries did not identify arrest rates for female juveniles during the period.

Further consequences of opioid dependence include poor self-care, nutritional imbalance, impairment of family and community support systems, loss of housing, and financial difficulties, of varying severity. Thrill seeking and experimentation contribute to initial opioid exposure, evidenced by the marketing of street opioids with ominous names: "DOA," "Body Bag," "Instant Death," and "Silence of the Lamb." Rather than scaring off young initiates, the implied danger seems to actually increase the drug's allure.

The rate of co-occurring opioid abuse and mental health disorders in the United States ranges between 29 % and 59 % of opioid addicts (Kessler, 1995; Regier et al., 1990). This comorbidity is associated with poor prognosis and with "revolving door" treatment admissions (Haywood et al., 1995). Antisocial personality disorder may not predate the development of opioid dependency, but such a disorder frequently develops because of the pharmacological effects of opioid abuse, along with the high costs in obtaining the drug (Belkin, Gold, 1991). It was suggested that development in all areas of the abuser's life, including education-vocational, sociological, and psychosexual, is impaired and delayed as a consequence of the dependence.

Opioid Treatment Options

Many opioid abusers do not need treatment. Those users who are not dependent and use only occasionally, may decide to stop using without intervention. Factors influencing the decision to stop using include perception of a social environment that is intolerant toward drug use, the threat of social, legal and employer sanctions, and dawning perception of risks associated with drug abuse (U.S. Office of National Drug Control Strategy, 1990). Treatment is for those who cannot stop illicit drug use without help, usually those who have become dependant upon their drug, or drugs, of choice to manipulate emotions, cope with stress and uncomfortable feelings, feelings of personal inadequacy, or depression when not using (Breshner, 1986; Jaynes and Rugg, 1988; MacDonald, 1989; Nowinski, 1990). It has long been established (Hser, et al, 2001, 1995; Haywood et al., 1995) that treatment of some sort results in harm reduction for opioid addicts.

In 1999, the Center for Substance Abuse Treatment (U.S. Department of Health and Human Services, 1999b) proposed that a comprehensive treatment program should include at least eighteen focus elements. First there should be an assessment, including a medical examination, drug use history, psychosocial evaluation, and, where warranted, a psychiatric evaluation, as well as a review of socioeconomic factors and eligibility for public health, welfare, employment, and educational assistance programs. The assessment should be followed by same day intake, to maintain the client's involvement and interest in treatment. At the time of intake and assessment, the clinician conducting intake should document findings and develop with the client an initial treatment plan, to enhance clinical case supervision.

The client should have access to preventive and primary medical care, preferably provided on site. There should be provision for testing for infectious diseases, at intake and at intervals throughout treatment, for infectious diseases, including hepatitis, retrovirus, tuberculosis, HIV/AIDS, syphilis, gonorrhea, and other sexually transmitted diseases. The client should undergo frequent random drug testing, no less often than weekly, to ensure abstinence and compliance with treatment.

The program should include regularly scheduled group counseling interventions, to address the unique emotional, physical, and social problems of the client. The program should provide substance abuse counseling, including psychological counseling, psychiatric counseling, and family or collateral counseling provided by persons certified by State authorities to provide such services.

Clients should have access to ancillary services including practical life skills counseling, including vocational and educational counseling and training, frequently available through linkages with specialized programs. Clients should receive general health education, including nutrition, sex and family planning, and HIV /AIDS counseling, with an emphasis on contraception counseling for adolescents and women. Clients should receive information about and referral to peer/support groups, particularly for those who are HIV-positive or who have been victims of rape or sexual abuse.

The program should provide liaison services with immigration, legal aid, and criminal justice system authorities. Clients should be encouraged to explore social and athletic activities, to retrain clients' perceptions of social interaction. Clients should have access to alternative housing for homeless clients or for those whose living situations are conducive to maintaining the addictive lifestyle.

The program should provide relapse prevention education, which combines aftercare and support programs, such as Alcoholics Anonymous and Narcotics Anonymous, within an individualized plan to identify, stabilize, and control the stressors which trigger and ring about relapse to substance abuse.

Staff should receive on-the-job staff training and education. Staff should frequently document the client's progress. Clinical supervisors should conduct frequent review of the client's treatment plan and progress, to enable refinement and improvement of service delivery.

Finally, and of particular importance to opioid dependent populations, the program should include pharmacotherapeutic interventions, by qualified medical practitioners, as appropriate for those, those addicted to opioids, clients having mental health disorders, and HIV-seropositive individuals.

Between 1851 and 1865, opioid abusers in California were primarily immigrants or users of patent medicines that contained a tincture of opium. In 1806, morphine was isolated from opium, followed in the isolation of codeine in 1832. and papaverine in 1848. All three were used extensively for pain relief during the U.S. Civil war, facilitated by injection though the hypodermic syringe, invented in 1853, and were abused by veterans, along with opium, creating California's first major wave of addiction to injectable narcotics, though the turn of the century. The penultimate improvement in morphine delivery was the synthesis of Heroin, from morphine, by Beyer Pharmaceuticals in 1908. From the experiences of those treating that first wave of injected opioid abusers, two treatments emerged, forced withdrawal and graduated withdrawal by dose reduction of the abused drug, usually in an institutional setting. According to an NIDA Infofax (NIDA, Heroin #13548), the effect of:

> "Withdrawal, which in regular abusers may occur as early as a few hours after the last administration, produces drug craving, restlessness, muscle and bone pain, insomnia, diarrhea and vomiting, cold flashes with goose bumps ('cold turkey'), kicking movements ('kicking the habit'), and other symptoms. Major withdrawal symptoms peak between 48 and 72 hours after the last dose and subside after about a week. Sudden withdrawal by heavily dependent users who are in poor health is occasionally fatal, although opioid withdrawal is considered much less dangerous than alcohol or barbiturate withdrawal."

Opioid dependent clients who present for treatment, have typically been abusing opioids for 5-8 years (Margolin, Kosten, 1991), and first must undergo a period of detoxification, either slow or rapid, during which the client experiences negative reinforcement arising from craving for opioids in the opioid receptors in the locus coeruleus mesolimbic centers of the brain and in opioid receptors throughout the body. According to Margolin and Kosten, the withdrawal process is characterized by fear and anxiety, thermal deregulation, gastrointestinal distress, sleep and appetite distress. The client experiences these changes as extremely distressing.

There have been attempts to develop detoxification procedures to dampen the excitation of the locus coeruleus caused by absence of introduced opioids and to compress the time required to normalize body homeostasis and sustain the clients' motivation to stop using drugs.

Prior to 1965, treatment for opioid dependence, in California, generally involved either slow withdrawal by administration of reduced dosages of morphine, or more rapid forced withdrawal, involving restraints, palliative medications, and close monitoring. The follow-up abstention, with or without social support, meeting attendance, or behavioral modification. Narcotic substitution therapy, of which methadone maintenance is the most popular modality, followed by LAAM (L-alphaacetylmethadol), was first introduced in 1963 by Dole and Nyswander (Dole and Nyswander, 1965). By 1990, according to Margolin and Kosten, detoxification centered upon either slow tapering withdrawal through substitution of methadone or LAAM, or rapid detoxification through induction of naltrexone. Recently, Buprenorphine substitution has been advanced.

Rapid and Ultrarapid Detoxification Through Naltrexone Induction

A treatment that has gained popularity with managed care providers and clients who find methadone/LAAM maintenance undesirable, is rapid (ROD) and ultrarapid opioid detoxification (UROD) through clinics that promise quick, painless, same-day detoxification followed by oral naltrexone therapy. According to one review (O'Conner, Kosten, 1998), general anesthesia is given via endotracheal tube, and then high dose naltrexone, an opioid antagonist, is induced. Withdrawal occurs within four to five hours and the client usually awakens without opioid dependency. The client is then started on oral naltrexone and any subsequent, persistent withdrawal symptoms are treated symptomatically. In theory, this results in continuous therapeutic levels for this drug, and avoids issues with noncompliance.

Naltrexone is used because it blocks the euphoric effects of opioid use and discourages recidivism. In addition, evidence exists that it blunts drug craving. Although the mechanism is not entirely clear, the speculation is that receptor occupancy by an antagonist, driving out naturally occurring and induced opioids, is sufficient to blunt cravings. The transition from drug withdrawal or abstinence to naltrexone maintenance must be made as rapidly as possible, as patients frequently relapse during this phase.

Furthermore, according to O'Conner and Kosten, data from early studies suggested that when high-dose opioid antagonists induced withdrawal, symptoms were greatest within the first few hours of treatment and declined to tolerable levels rapidly. Some studies (Albanes, et al, 2000), however, demonstrate that withdrawal symptoms persist for up to one week after rapid detoxification.

According to Albanes et al, most of the early investigations focused on rapid withdrawal and transition report success with this process and tout it as a safe, comfortable, same-day, outpatient treatment for heroin addiction. This has led to a proliferation of ROD and UROD drug treatment centers in major urban areas that are widely advertised-on television, in newspapers, in magazines, on billboards and on the Internet. Albanes et al suggest this marketing appeals to those with private insurance and the desire for rapid, successful treatment by clients who have otherwise been unable to abstain. Most studies suggest that when the detoxification procedure is physiologically successful as measured by the response to antagonist challenge, recidivism ranges from 10 % to 50 %.

In addition, the outpatient nature of UROD may lead to diminishment of the importance of continued medical and psychosocial support to ensure success. These patients are sent home with a large number and variety of potent medications to counter the continued withdrawal symptoms, including clonidine, baclofen, octreotide, ondansetron, benzodiazepines, and trazodone-with little ongoing therapy provided by the centers.

Clients who do not successfully transition to oral naltrexone therapy may present to emergency medical facilities for treatment of complications, including acute dyspnea vomiting and aspiration of vomitus, diarrhea, dry mouth, weakness, fatigue, poor urine output, and hyperalgesia, acute pulmonary edema anxiety, generalized tonic-clonic seizures, anorexia and 15 to 20 pound weight loss, chills, coughing, abdominal pain, twitching, frothy salivation at the lips, high fevers, high blood pressure and ultrarapid pulse, bleeding esophageal varices dehydration, and toxicity of supportive chronic sneezing and drug therapy (baclofen). Effects of UROD on preexisting medical conditions include bleeding esophageal varices (perhaps induced by recurrent vomiting) and withdrawal from cross-addictions not treated by UROD therapy. Most ROD and ROD programs do not address concurrent dual addiction issues or drug education and relapse prevention.

There are reports of death, prolonged respiratory depression, and persistent withdrawal symptoms. Albanes et all stated a limited number of reports also suggest that the use of naloxone may be associated with pulmonary edema, perhaps due to the excessive release of catecholamines during unrecognized hypercardia from hypoventilation. In addition, patients may titrate opioid use to higher doses to overcome the naltrexone effect.

Slow Detoxification through Methadone, LAAM and Buprenorphine

According to the National Association of Methadone Advocates (NAMA, 2003) Methadone is a synthetic narcotic analgesic compound that was developed in Germany in the 1940s. The drug effectively suppresses the craving for heroin without the euphoric effects of heroin. Methadone has a half-life of about 24 hours and when the right therapeutic dosage is administered, patients only require the drug once per day. In clinics, Methadone is administered orally. Maintenance dosages of 80 - 120 mg produce pharmacological cross-tolerance, so if the methadone patient uses heroin, the euphoric effects are not experienced. Methadone is relatively safe and non-toxic and it has minimal side effects. It is most effective when used in conjunction with medical treatment, rehabilitation and counseling. Absorption, metabolism and excretion can vary significantly from person to person, so methadone doses should be individualized so that appropriate amounts are administered. Alan E. Peters, M.D. PhD, with Kingsview Behavioral Health Programs, Mariposa and Sonora CA, reports that studies have shown a strong negative correlation between methadone dosage and the amount of concurrent illicit drug use. He suggested that if the body were being afforded insufficient dosage to handle the withdrawal, patients would substitute to ease the suffering.

NIDA (NIDA, 2003) reports that studies dating back to the 80s have found that 65-85% of people undergoing methadone maintenance stays in treatment for a year or more. The longer patients stay on Methadone, the better they look on a number of variables. Its research has suggested that patients show a marked decrease in criminal behavior and an increase in employment during their time in treatment. Methadone maintenance reduces the risk of AIDS infection, as those undergoing methadone maintenance are less likely to concurrently inject and are therefore not engaging in such practices as needle sharing. Patients can be treated safely with methadone for 15 or more years. NIDA also proposed that the most important medical consequence of chronic methadone maintenance treatment is a marked improvement in the client's general health and nutrition.

NIDA reported on the cost effectiveness of methadone maintenance when compared to other treatment modalities: Over a 6-month period the costs of an imprisoned drug abuser are about $20,000; for addicts involved in inpatient or residential treatment the cost is between $8,000 - $9,000. Methadone treatment and outpatient counseling treatment were about tied at $17,00 for the former and $1,500 for the latter.

As an opiate, regular use of methadone causes physical dependency. Once the user stops, the user will experience a withdrawal. The physical changes due to the drug are similar to other opiates, including suppressed cough reflex, contracted pupils, drowsiness and

constipation. Alan Peters noted that some methadone users feel sick when they first use the drug. A woman using methadone may not have regular periods, is still able to conceive. Methadone is a long-acting opioid; it has an effect for up to 36 hours and can remain in the body for several days.

The primary advantage of long-term or extended detoxification is that the client's body normalizes in small increments, each of which, according to Dole and Nyswander, is relatively painless. Margolin and Kosten suggest the risks associated with slow detoxification include decline in the client's motivation to ultimately abstain, resulting in maintenance of up to 37 years (so far) and increased relapse potential if concurrent psychosocial issues are not addressed. In a private conversation with Tracy Franco, RN, a clinical supervisor at a large chain methadone clinic in Stockton, CA, March 22, 2003, she confirmed that 65 % of the 479 clients served at the single facility have been on methadone maintenance for over 10 years, and refuse to accept reduction in dosage below 65 mg methadone, a dosage having approximately the same effect as the usual street dose of Heroin available in the San Joaquin Valley.

Arthur Schubert, former clinical director at St. Joseph Hospital of Stockton's drug treatment program, stated methadone is dissolved in a flavored liquid, and is administered to patients daily, under observation. Long-standing program participants are allowed "take-home" doses of methadone hydrochloride, which they may self-administer. Doses of methadone usually range from 20 to more than 100 mg per day. Higher doses are shown to be generally associated with better retention in treatment. Urine toxicologic screening is performed randomly and periodically to assess compliance with treatment. Counseling and other rehabilitative services are provided on a regular basis.

Tracy Franco, in private conversation, reported that her employer provides only basic relapse prevention and drug education or psychosocial counseling. She confirmed the client population frequently suffers from untreated polydrug abuse, particularly cocaine or methamphetamine, and that her agency has stopped authorizing take home doses to prevent sale or misuse of the drug. Further, she stated her experience that the daily dosing of opioid addicts switched to methadone resulted in high dropout rates among clients and in long-term habituation to the drug among those who stayed in the program. Margolin and Kosten (1991) reported what while 80% of methadone users can complete a program of detoxification, if challenged by a naloxone dosing within three months, 60 % would show positive for opioids and 80 % would relapse within three years.

In a randomized controlled study of 150 opiate-dependent patients (Azar, 1998), the researchers found that treatment was more successful for heroin addicts who visited a treatment clinic two days a week than for those who visited the clinic five days a week. They randomly assigned patients to four groups that received 50 mg or 80 mg of methadone and attended a clinic two or five days a week. Patients who visited the clinic two days a week had a lower dropout rate and used less heroin than patients who had to visit the clinic five days a week. Even those who received 50 mg, a methadone dose generally regarded as inadequate—were less likely to drop out if they were assigned to twice-weekly visits as opposed to five-day-a-week visits. Ms. Franco suggested that in her experience, opioid craving would develop within 48 hours and after 72 hours she would expect dropout or relapse risks to increase. An opioid substitute that would permit less frequent dosing is LAAM (levoalphaacetylmethadol).

LAAM is a synthetic opioid agonist approved by the Food and Drug Administration (FDA) in July 1993 and commercially available since August 1993. Like methadone, LAAM creates a pharmacologic cross-tolerance to other opioids and therefore blocks the euphoric effects of those drugs while also controlling opiate craving. While Methadone suppresses opiate withdrawal symptoms for 24 hours or longer, LAAM achieves this effect for 48 to 72 hours or longer.

Because of LAAM's long duration of action, after a patient's tolerance to LAAM has been established, it can be administered no more frequently than every other day. In humans, LAAM is metabolized into two active metabolites, nor-LAAM and dinor-LAAM. Both are metabolized more slowly than the parent drug. It is believed that this slow metabolism is the basis for LAAM's long duration of action. Like methadone, LAAM is similar in action to morphine. Its effects include analgesia, sedation, and respiratory depression. Tolerance to these effects develops with prolonged use, and an abstinence syndrome similar to that observed with morphine and other opiates occurs with cessation of regular use. However, with LAAM, the syndrome has a slower onset and lasts longer, with less acute symptoms. This slower onset contributes to higher initial dropout rates than in methadone program, with a corresponding higher relapse rate (Woody, O'Brien, 1991).

The California ADP Executive Summary for 2003 states that 33 % of California programs involved in drug substitution in opioid treatment use methadone only, 66 % use both methadone and LAAM and no programs use LAAM only. Programs using clonidine, naloxone, buprenorphine or other drugs in treatment were not considered statistically significant.

Buprenorphine and Buprenorphine /Naloxone Treatment in Opioid Treatment

Researchers have considered buprenorphine as a treatment for opioid dependency as early as 1978 (Jasinski, et al, 1978), when its abuse potential was researched. LAAM and methadone are complete opioid agonists, while buprenorphine is an opioid partial agonist and partial antagonist. This means that, although buprenorphine is an opioid, and thus can produce typical opioid agonist effects and side effects, such as euphoria and respiratory depression, its maximal effects are less than those of full agonists like heroin and methadone. According to Reckitt Benckiser, the manufacturer of the buprenorphine monotherapy product, Subutex, and a buprenorphine/naloxone combination product, Suboxone, at low doses, buprenorphine produces sufficient agonist effect to enable opioid-addicted individuals to discontinue the misuse of opioids without experiencing withdrawal symptoms. The agonist effects of buprenorphine increase linearly with increasing doses of the drug until at moderate doses they reach a plateau and no longer continue to increase with further increases in dose, a so-called "ceiling effect," which discourages abuse of the drug. Thus, buprenorphine carries a lower risk of abuse, dependence, and side effects compared to full opioid agonists. In fact, in high doses and under certain circumstances, buprenorphine can actually block the effects of full opioid agonists and can precipitate withdrawal symptoms in an acutely opioid-intoxicated individual.

Suboxone, the product containing naloxone, was formulated to both increase opioid antagonist effects, and to reduce cravings for both opioids and concurrently abused drugs particularly cocaine. In working with my court-mandated (Proposition 36) clients, I found one (of three opioid dependent clients on my caseload) who had a history of five methadone treatment failures in the past 13 months. This client was able to reduce opioid dependence to 35 mg daily but was unable to resist snorting cocaine for over 96 hours at a time. I was able to help him find a certified physician in Stockton, CA (the only certified provider in the 209 area code), who placed him on Suboxone in early February 2003. This client has been on the treatment nearly 60 days and has returned seven consecutive clean (for cocaine) urinalysis screens, a personal best. This client claims reduction in cravings to a manageable level, so far. While this is neither statistically nor longitudinally significant, I find it promising to help this client in becoming drug free.

According to Reckitt Benckiser, buprenorphine has poor oral bioavailability and moderate sublingual bioavailability. For this reason, the FDA approved formulations for opioid dependence treatment are in the form of sublingual tablets. The half-life of buprenorphine is 24–60 hours, meaning that unlike methadone, and like LAAM, it can be dispensed every two or three days with low likelihood of craving developing and relapse during treatment. The maximal effects of buprenorphine appear to occur in the 16–32 mg dose range for sublingual tablets.

Higher doses are unlikely to produce greater effects. Respiratory depression from buprenorphine (or buprenorphine with naloxone) overdose is less likely than from other opioids. There is no evidence of organ damage with chronic use of buprenorphine, although increases in liver enzymes are sometimes
seen. Likewise, there is no evidence of significant disruption of cognitive or psychomotor performance with buprenorphine maintenance dosing.

Side effects of buprenorphine are similar to those of other opioids and include nausea, vomiting, and constipation. Buprenorphine and buprenorphine/naloxone can precipitate the opioid withdrawal syndrome. Additionally, the withdrawal syndrome can be precipitated in individuals maintained on Buprenorphine, to the extent dependence exceeds the maximal dosing of 30 mg daily. Signs and symptoms of opioid withdrawal include dysphoric mood, nausea or vomiting, muscle aches/cramps, lacrimation, rhinorrhea, pupillary dilation, sweating, piloerection, diarrhea, yawning, mild fever, insomnia food and drug craving, and distress/irritability. A chain of methadone clinics, Narconon, Inc., (Narconon, 2003) claims diverted buprenorphine has been involved in over 100 deaths, in France, without substantiation. Other literature (Chedderton, 2000) reports buprenorphine has been used in preference to methadone in opioid dependence treatment in France, with over 50,000 clients in regular treatment, as opposed to 6,000 on methadone treatment, and that buprenorphine had a better safety profile than methadone.

In 2001, H. Westley Clark, M.D., gave a keynote address to the30th Summer Clinical Institute in Addiction Studies at UC San Diego, in which he suggested that the administration of buprenorphine through primary care physicians, in office visits, would permit effective, cost-effective and compassionate treatment for opioid dependence without the stigma attached to daily dosing at methadone clinics. He stated that the U.S. Department of Health and Human Services was working closely with Rickitt & Coleman (now Rickitt Benkiser) in a cooperative research agreement to bring about approval of the drug by the FDA and to train physicians in its administration. He commented that in the future treatment for opioid drug dependency, in fact all drug dependency, would be seen as 60 percent treatable with drug interventions and 40 percent treated by behavioral modification, and much of that modification could also occur in the treating physician's office.

According to Reckitt Benckiser, buprenorphine is abusable, particularly by individuals who are not physically dependent on opioids. Naloxone is added to buprenorphine to decrease the likelihood of diversion and abuse of the combination product. Sublingual buprenorphine has moderate bioavailability, while sublingual naloxone has poor bioavailability. Thus, when the buprenorphine/naloxone tablet is taken in sublingual form, the buprenorphine opioid agonist effect predominates, and the naloxone does not precipitate opioid withdrawal in the opioid-dependent user. Naloxone via the parenteral route, however, has good bioavailability. If the sublingual buprenorphine/naloxone tablets are crushed and injected by an opioid-dependent individual, the naloxone effect predominates and can acutely precipitate the opioid withdrawal syndrome.

Under certain circumstances buprenorphine by itself can also precipitate withdrawal in opioid-dependent individuals. This is more likely to occur with higher levels of physical dependence, with short time intervals (e.g., less than 2 hours) between a dose of opioid agonist (e.g., methadone) and a dose of buprenorphine, and with higher doses of buprenorphine.

European and Australian studies (Agar, et al, 2001) have shown that buprenorphine is more effective than placebo and is equally as effective as moderate doses of methadone and LAAM in opioid maintenance therapy. Buprenorphine is unlikely to be as effective as more optimal-dose methadone, and therefore may not be the treatment of choice for patients with higher levels of physical dependence. It might be noted that Margolin and Kosten (1991) suggested buprenorphine at 30 mg would be effective in opiate detoxification of "usual street

doses" of Heroin or the equivalent dose of methadone, but increases in the purity of street Heroin have increased the street dose to 65-90, mg, at which point more severe withdrawal symptoms would occur.

According to U.S. Department of Health and Human Services literature (U.S. Department of Health and Human Services, 2003a, 2003b), few studies have been reported on the efficacy of buprenorphine for completely withdrawing patients from opioids. In general, the results of studies of medically assisted withdrawal using opioids (e.g., methadone) have shown poor outcomes. Clients switched to buprenorphine from high methadone dosages may suffer withdrawal to buprenorphine's effective ceiling level of 30-35 mg. Buprenorphine, however, is known to cause a milder withdrawal syndrome compared to methadone and for this reason may be the better choice if opioid withdrawal therapy is elected, once the client has been partially detoxified with methadone, or LAAM, to the level that a 30 mg or lower dosage of buprenorphine will be tolerated.

There potential advantages in using buprenorphine. First, it appears to have a better safety profile in overdose. Secondly, many clients may be dosed on alternate days without experiencing withdrawal symptoms. Thirdly, there is some evidence that clients find it is easier to withdraw from buprenorphine in comparison to methadone. Finally, a number of clients report feeling less sedated on buprenorphine than on methadone. When used in conjunction with naloxone, opioid antagonist qualities are enhanced and craving for opioids and other frequently abused drugs is greatly reduced.

Availability of Drug Substitution Therapies in Selected California Counties

As of April 3, 2003, California has authorized 143 facilities to treat 41,336 opioid dependent clients, at 143 facilities (ADP, 3003). 83 facilities are licensed to administer both methadone and LAAM, while 60 facilities administer only methadone, and no facilities treat with LAAM only. 130 physicians statewide are certified to administer buprenorphine to up to 3,900 opioid dependent clients.

Three facilities in San Joaquin County are licensed to treat 1,650 opioid dependent clients, with one facility, operated by Aegis Medical Systems, authorized to used methadone and LAAM. One physician in Stockton is certified to administer buprenorphine to up to 30 clients. The physician, Randell L. Stenson, M.D., reports treating 25 clients.

In Stanislaus County, two clinics are authorized to treat up to 650 opioid dependent clients, with Aegis Medical Systems operating a clinic licensed for LAAM and methadone. No physicians are reported to be certified to treat with buprenorphine.

In Mariposa, Amador, Calaveras, and Tuolumne Counties, four rural counties with similar populations and often grouped as "MACT," no facilities or physicians are licensed to treat opioid dependency with drug substitution. In Amador, Mariposa, and Tuolumne Counties, the county general hospitals, and in Calaveras County St. Joseph's Hospital, detoxify 24-45 opioid overdoses each year with short-term clonidine and naltrexone therapy, and then refer the users to the county alcohol and drug programs. According to Rita Austin, LSCW, Director of Calaveras County ADP, Amador and Calaveras contract with San Joaquin County for treatment of opioid users, while Tuolumne County contracts with Stanislaus County, and Mariposa County contracts with Merced County for its opioid users who are ordered to attempt treatment.

Barriers Limiting Implementation of Subutex and Suboxone in the Target Counties

Just over two months have elapsed since Subutex and Suboxone have been shipped to pharmacists for prescription by physicians, in their offices. Some California physicians, mostly psychiatrists and specialists in addiction medicine, have certified to prescribe the drug. The response in Amador, Calaveras, Mariposa, San Joaquin, Stanislaus, and Tuolumne Counties has been largely nonexistent.

Representatives of Amador County and Mariposa County Alcohol and Drug Programs

Declined to be interviewed for this study. Rita Austin, with Calaveras County, cited the relatively low incidence of opioid dependency in Calaveras County, compared with high methamphetamine, cannabis, and alcohol addictions, as a primary barrier to the county spending drug treatment funds on a public clinic, and opposition through zoning and licensing as a ground for opposition to a for-profit or non-profit organization establishing a treatment center. Ms. Austin agreed that an in-office treatment program through physicians, accompanied by drug education, harm reduction and behavioral counseling would be preferable to establishment of methadone clinics. Nonetheless, she expressed doubt that the County would approve such programs. Jack Steele, with Changing Echoes, the sole residential drug treatment facility in the county, advised that treating opioid addicts had been considered but that county requirements for supervision and monitoring outpatient or residential clients in withdrawal were cost-prohibitive. He stated he might be interested in working with a physician trained to administer Buprenorphine, if there was a proven need for services.

Julia Davis, with Kingsview Behavioral Health Services, which operates the Tuolumne County Alcohol and Drug Programs, stated her employer, which has recently laid off 45 percent of its treatment staff, would have no interest in applying to the County for drug substitution treatments. She cited opposition by the County Board of Supervisors to funding or maintaining talk-therapy outpatient care for addicts, let alone any modality that might have side effects or might encourage Heroin addicts to come to Tuolumne County. Alan E. Peters, M.D., who until recently contracted with Kingsview, stated he might certify to administer Buprenorphine, if there was a need. Maynard's Treatment Centers declined a request for an interview, except to say it would offer 28-day services to opioid addicts who had detoxified and stabilized, but considered addicts in withdrawal to be unsuitable for its programs.

Lisa Schnepple, with San Joaquin County Alcohol and Drug Programs, stated she was unaware of a physician treating opioids dependency with buprenorphine in Stockton, but felt methadone/LAAM treatment options in the county were satisfactory. She had no knowledge of the clinical studies in using buprenorphine in treatment.

In Modesto, Mirabelle Ortega, Stanislaus County Alcohol and Drug Services, suggested that the county might welcome a treatment that might reduce polydrug problems in opioid withdrawal programs. She was not aware of the studies made for Buprenorphine treatment or that it was an approved option.

Religious opposition to implementation of buprenorphine treatment in the selected counties
appears to generally follow moral attitudes regarding chemical dependency and drug–based treatment in general. Katherine Brenson, a minister and non-drug healer in Twain Harte, suggested that most religious groups would not actively oppose physicians from prescribing Buprenorphine from their offices, to small client populations, but might become more concerned with high volume methadone clinics in residential areas.

Paul Patterson, a minister who works with substance-dependent adolescents in Stanislaus County and San Joaquin County, suggested that in urban counties appreciation of the benefits of drug-substitution treatment would outweigh faith-based opposition, while in rural counties, particularly Tuolumne County, where most health care is under patronage of Adventist health care, opposition would be greater. Carole Alton, with the Adventist Regional Medical Center in Sonora, formerly Sonora Community Hospital, reported that the center has taken the official position not to participate in drug treatment for addictions, leaving it to the county hospital. She declined to comment on sanctions that might be imposed on physicians who might certify to prescribe buprenorphine. Richard Behymer, M.D., in Sonora, stated that the Adventist hospital has traditionally opposed use of opioids for long-term pain management, and has screened physicians seeking privileges regarding prescription of opioids or scheduled drugs.

Larry Arroyo, with M.A.C.T. tribal clinics in the four rural counties, stated a policy to encourage non-drug interventions in treatment of addictions. “Heroin addiction is not an Indian disease, and we have not been faced with treating our members for it.” He suggested that if the need arose, the clinics would refer to physicians who were certified to use buprenorphine.

Opposition from methadone/LAAM providers in Stanislaus and San Joaquin Counties was nominal. The counties provide methadone only treatment, and as stated above, expressed no opposition to clients who wanted alternative treatment from physicians from receiving it. Aegis Medical Systems, which operates the methadone/LAAM clinics in the two counties, declined to discuss buprenorphine treatment. Tracy Franco, suggested the provider does not perceive in-office treatment as a viable alternative to its clinic practice, which are large and well established in the counties.

Narconon, which operates methadone/ LAAM clinics in California, an in other states, does advertise on its website certain death risks associated with abuse of buprenorphine, as stated above.

H. Westley Clark, speaking at the 30th UCSD Clinical Institute, suggested in 2001, that methadone clinics could be expected to oppose office-based opioid dependency treatment because, methadone clinics treat both new patients and patients who have been stabilized to methadone. New users take a disproportionate economic toll on the program. Stabilized users provide economic continuity to the program. However, stabilized users are the ones most likely to be suitable for buprenorphine treatment and, therefore, are most likely to leave the program in favor of office based treatment.

Under the DATA 2000 law, physicians are required to have a minimum of eight hours of training to prescribe buprenorphine, and must obtain a waiver from the DEA. Physicians who are already certified as addiction specialists are exempt from the training requirements.

Richard Behymer, M.D., suggested the largest barrier to implementation would come from physicians themselves. Even with the new regulations allowing doctors to prescribe, they're not going be in a hurry to certify. Most physicians don't want addicts as patients. The idea of keeping addicts in the office for half-an hour waiting for the drug to take effect is not attractive for them. He suggested most physicians who do certify will be those already involved in drug treatment as certified specialists. Moreover, many physicians will remain reluctant to either provide or refer users to talk-therapy programs, as is mandated by the law. Finally, the 30-client limit on the number of patients served does not appear to make the program economically attractive.

Conclusions

Buprenorphine has been approved for treatment of opioid dependency, in physician’s offices. It appears to be an effective harm-reduction treatment to assist in drug substitution, gradual detoxification and craving reduction. With over 150,000 opioid abusers in California, 30,000-40,000 of whom are seeking treatment, many of whom are poly-drug addicted, the monotherapy and polytherapy formulations appear to be needed. The literature indicates Buprenorphine to bee effective in treatment with generally acceptable side effects and a lower potential for abuse than methadone.

It is too early to determine how effective it will be as a treatment in California, which has a well established base of methadone clinics. The barriers to implementation of the drug appear insignificant, once physicians are trained in its use and are willing to engage in drug-substitution therapy. More research needs to be undertaken to determine addict attitudes and physician attitudes toward implementation of harm reduction and slow detoxification in physician’s offices.

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