SUPPLEMENT TO THE FINAL SUMMARY REPORT FROM THE SAMHSA EVALUATION OF THE BUPRENORPHINE WAIVER PROGRAM:

AN UPDATED LITERATURE REVIEW*

BACKGROUND AND PURPOSE

On October 17, 2000, President Bush signed into law The Drug Addiction Treatment Act of 2000 (DATA), Title XXXV, Section 3502 of the Children's Health Act of 2000. DATA expands the clinical context of medication-assisted treatment by allowing qualified physicians to dispense or prescribe specifically approved Schedule III, IV, and V narcotic medications for maintenance treatment and detoxification. In addition, DATA reduces the regulatory burden on physicians by permitting qualified physicians to apply for and receive Waivers from the special registration requirements defined in the Controlled Substances Act. Upon approval by the Food and Drug Administration (FDA) on October 8, 2002, two formulations of buprenorphine, Subutex® and Suboxone®, became the first medications eligible for use under the DATA physician Waiver program, and currently they remain the only medications available for the maintenance or detoxification treatment of opioid dependence or addiction.

DATA specifies that the Secretary of Health and Human Services (HHS), may make determinations as to whether:

- maintenance treatment and detoxification provided under the program of Waivers have been *effective* forms of treatment in clinical settings;
- whether such Waivers have significantly increased (relative to the beginning of such period) the *availability* of maintenance treatment and detoxification treatment; and
- whether such Waivers have adverse consequences for the public health (e.g., adverse consequences, diversion for abuse).

Based on their determinations concerning these three points, the Secretary may decide whether the Waiver Program should continue and, if so, whether program standards and requirements should be revised.

SAMHSA conducted a three-year, national evaluation of the impact of the Waiver program, which concluded in November, 2005. To assure that all relevant information was captured in the evaluation, in February 2006 SAMHSA commissioned an additional literature review by JBS International, Inc. The results of that analysis are summarized below as a supplement to the final report on the SAMHSA Evaluation of the DATA Waiver Program.

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METHODS

Literature published in the interval following Westat's initial literature review (that is, literature published between late 2004 and February 2006) was the subject of a PubMed search by a JBS Substance Abuse Library Information Specialist (SALIS). The search (using the key words "buprenorphine," "Buprenex," "Suboxone," and "Subutex") yielded 347 articles published in peer-reviewed journals. On review, approximately half the articles were excluded from the review because they were not relevant to the Evaluation of the Buprenorphine Waiver Program.

A separate search – using the same key words but focused exclusively on reports from outside the U.S. – was conducted through the library at England's Cambridge University. The international literature was considered essential to this review because buprenorphine has been used in the treatment of addiction much longer in some foreign countries than in the U.S., offering a rich body of experience and possibly early indicators of issues that may emerge as the U.S. Waiver Program matures.

The resulting literature was analyzed by an experienced reviewer and submitted to a group of expert consultants for peer review.

FINDINGS: EFFECTIVENESS OF BUPRENORPHINE

There are several potential mechanisms by which medications may interrupt addictive behaviors, including suppression of craving, relief of withdrawal symptoms, reduction of drug-seeking behavior, and targeting risk factors specific to particular subgroups (such as family history of addiction, novelty-seeking/impulsiveness, etc.) (Heidbreder & Hagan, 2005). Buprenorphine, a derivative of thebaine, is a high-affinity, partial mu agonist with kappa antagonist action. This unique combination of pharmacologic properties is thought to offer significant advantages over existing medications for the treatment of opiate addiction (Sporer, 2004). Specifically, buprenorphine is able to block the effects of opiates such as morphine, while offering opiate-like effects that appear likely to encourage better compliance than would a non-opiate or opiate antagonist (Vocci & Ling, 2005).

Metabolism. Buprenorphine is well-absorbed sublingually, with the sublingual form offering 60 to 70 percent of the bioavailability of intravenous administration (Vocci, Acri et al., 2005). The sublingual form results in bioavailability about twice that of orally ingested buprenorphine (Jenkinson, Clark et al., 2005). The drug is lipophilic, and brain tissue levels far exceed serum levels. It is highly bound to plasma protein and is inactivated by enzymatic transformation via N-dealkylation and conjugation (Elkader & Sproule, 2005). Buprenorphine is widely distributed, with peak plasma concentration occurring at about 90 minutes and a half-life of 4 to 5 hours. It is metabolized mainly to inactive conjugated metabolites (Sporer, 2004).

While buprenorphine dosage does not need to be significantly adjusted in patients with renal impairment, it is possible that the metabolism of buprenorphine is altered in patients with severe liver disease because CYP3A4 activity may be decreased. Although only limited evidence is available in the literature, drugs that are known to inhibit or induce CYP3A4 have the potential to enhance or reduce buprenorphine N-dealkylation (Elkader & Sproule, 2005).

The presence of naloxone does not appear to influence the pharmacokinetics of buprenorphine. The rationale for adding naloxone to one formulation was that naloxone's antagonist actions would produce a drug that is less subject to diversion and abuse. The 4:1 ratio of buprenorphine to naloxone was chosen because it produced significant attenuation of buprenorphine's effects without producing significant signs of withdrawal (Vocci, Acri et al., 2005).

Safety. The high-affinity blockade imposed by buprenorphine significantly limits the effects of subsequently administered opioid agonists or antagonists, and the "ceiling effect" appears to confer a high safety profile, a low level of physical dependence, and only mild withdrawal symptoms on cessation after prolonged administration (Vocci & Ling, 2005). In fact, sublingual doses up to 32 mg have been safely given to opiate-experienced – but not physically dependent – subjects (Sporer, 2004).

Buprenorphine's partial agonist properties also produce a ceiling effect on respiration, suggesting a lower risk of severe respiratory depression or apnea (Vocci & Ling, 2005).

Neri and colleagues (2005) found that buprenorphine produced approximately the same degree of immune system suppression as methadone, suggesting that both drugs stimulate hyperactivation of immune systems that may have been inhibited by heroin.

McKance-Katz (2005) examined the potential for drug interactions between buprenorphine and drugs used to treat HIV and hepatitis C – an important consideration, given the prevalence of these disorders in injecting drug users. She found that buprenorphine has a significant pharmacokinetic interaction with efavirenz (a frequent component of HAART) but no pharmacodynamic interaction, and concluded that simultaneous administration of the two drugs does not pose a risk of opioid withdrawal like that seen with co-administration of efavirenz and methadone. The author speculates that use of buprenorphine may simplify treatment of opiate-addicted patients with HIV disease and also improve clinical outcomes for persons infected with both HIV and the hepatitis C virus.

Buprenorphine is considered to be safe during pregnancy (Grimm, Pauly et al., 2005). In a prospective study of 260 infants born to 259 opiate-dependent mothers, three-fourths of the infants developed neonatal abstinence syndrome but none died, and the infants born to women treated with buprenorphine did as well as those whose mothers were treated with methadone (Lejeune, Simmat-Durand et al., 2005). Similar results have been reported in the U.K. (de Wet, Reed et al., 2005). In lactating women given buprenorphine at therapeutic levels, the concentration present in the breast milk was considered low (Grimm, Pauly et al., 2005).

Effectiveness. To examine the effectiveness of maintenance therapy using buprenorphine, Sullivan and colleagues (2005) used a cross-sectional and longitudinal analysis to study the clinical characteristics and outcomes of 96 patients entering a clinical trial of buprenorphine maintenance in a primary care clinic (PCC), compared to those of 94 patients receiving methadone maintenance in an opioid treatment program (OTP). They found that the PCC patients were more likely to be male (77 versus 55 percent), to have full-time employment (46 versus 15 percent), to have no history of methadone treatment (46 versus 61 percent), to have a shorter history of opiate addiction (10 versus 15 years), and to exhibit lower rates of injection drug use (44 versus 60 percent). The investigators concluded that office-based treatment with buprenorphine is associated with retention rates and treatment outcomes comparable to those of

methadone patients treated in OTPs (Sullivan, Chawarski et al., 2005). Similar results were reported by Marsch, Stephens et al. (2005).

Stein et al. (2005) also examined retention rates for patients treated with buprenorphine in a primary care setting. Using an observational cohort study of patients treated with buprenorphine /naloxone who were followed for 24 weeks, the investigators found that 59 percent of the patients remained in treatment at the end of the study period. Nearly half of the drop-outs occurred in the first 30 days. The variables most strongly associated with retention in treatment were abstinence during the first week of treatment, employment, and exposure to addiction counseling.

In a study designed to determine the optimal maintenance dose of the buprenorphine/naloxone combination product in heroin-addicted patients, Comer et al. (2005b) found that both the 8mg/2mg and the 32mg/8mg formulations were well-tolerated and effective at reducing the reinforcing and subjective effects of heroin, as compared with the 2mg/0.5 mg formulation. The investigators hypothesized that 80 to 90 percent of the mu receptors need to be inactivated in order to obtain significant reductions in heroin-induced effects.

Ling, Amass et al. (2005) compared the effectiveness of the buprenorphine/naloxone combination product with clonidine for opioid detoxification in both inpatient and outpatient community treatment programs. The investigators found that among the inpatients, 77 percent of those treated with the buprenorphine/naloxone combination achieved the defined treatment success criterion, compared to 22 percent of those given clonidine. Among the outpatients, 29 percent of patients given buprenorphine/naloxone achieved the success criterion, as opposed to 5 percent of those given clonidine. Ling and colleagues concluded that the results demonstrate clear superiority for buprenorphine /naloxone in the management of opioid withdrawal (Ling, Amass et al., 2005). Other investigators found similar results in a double-blind, placebo-controlled trial that compared buprenorphine with clonidine (both combined with behavioral interventions) for the treatment of adolescents (Marsch, Bickel et al., 2005).

In an examination of the effectiveness of buprenorphine treatment outcome in patients with co-occurring substance use and psychiatric disorders, Gerra and colleagues (2005) found that outcomes (as measured by treatment retention and illicit opiate use) were more significantly related to the psychiatric diagnosis than to the buprenorphine dose; that is, patients with a diagnosis of depression had the best outcomes at all doses of buprenorphine, while those diagnosed with antisocial or borderline personality disorder or schizophrenia had the least favorable outcomes. The investigators suggest that this may be because certain personality traits associated with the latter disorders – such as high levels of disinhibition, impulsiveness, and susceptibility to boredom – have been inversely related to treatment outcomes in other studies.

Amato and colleagues (2005) summarized the results of 52 original studies, involving 12,075 participants, which have been analyzed in five Cochrane Reviews of opioid substitution therapies. Thirteen of the studies (involving 2,544 participants) focused specifically on buprenorphine. After using statitistical analyses to calculate the weight of the findings for each of a number of outcomes (including retention in treatment, use of heroin or other drugs during treatment, and mortality), the investigators concluded that:

- *Retention*: Buprenorphine was less effective than methadone given in flexible doses, but there was no statistical difference in outcomes between high-dose methadone and low-dose buprenorphine.
- *Other drug use*: Methadone was more effective than buprenorphine (or any other pharmacotherapy) in preventing use of heroin or other drugs during treatment, especially when high doses were given.
- *Mortality*: Few studies reported this outcome. Among the five that did, the differences among treatment agents were not statistically significant.

Because many of the results found in this meta-analysis were dose-dependent, the investigators cautioned that they might be skewed in favor of methadone by the fact that methadone doses given in clinical trials probably are higher than those used in clinical practice (Amato, Davoli et al., 2005).

Researchers examined the difficulty of switching detoxification patients from methadone to buprenorphine. They found that all but 2 of the 23 study participants successfully completed the facilitated transfer, and concluded that transfer from daily methadone doses of 30 to 70 mg to buprenorphine in an inpatient setting is relatively uncomplicated and may be facilitated by use of lofexidine. This procedure, they suggest, may allow a larger number of opiate-addicted patients to access buprenorphine treatment (Glasper, Reed et al., 2005).

Few clinical trials have considered gender as a factor. However, in a trial that explored gender-based differences in response to opioid agonist therapies, Jones et al. (2005) found that the female subjects who received buprenorphine had less drug use than those who received methadone, while the male subjects who received LAAM had less drug use than those who received buprenorphine. Given the statistical significance of their results, the authors propose that clinical trials be designed to examine the impact of gender on treatment outcomes.

Summary. This review of the literature on the effectiveness of buprenorphine treatment for opioid dependence supports the conclusions of the Evaluation of the Buprenorphine Waiver Program that:

1. Multiple studies have shown that, administered sublingually and at therapeutic doses, buprenorphine is safe and effective.
2. Positive treatment outcomes were reported for patients treated with buprenorphine in office-based settings. Researchers have identified some patient variables that may prove useful in identifying those patients who are most likely to benefit from buprenorphine treatment.
3. Therapeutic outcomes for office-based treatment with buprenorphine are essentially comparable to those seen in patients treated with methadone in opioid treatment programs (OTPs).

FINDINGS: ACCESS TO MEDICATION-ASSISTED TREATMENT

Use of buprenorphine to treat opiate addiction in office-based practice has been widely expected to bring patients who have never before received pharmacotherapy into treatment (Bearn, de Wet et al., 2005). To test the actual experience to date, Sullivan and colleagues (2005) used a cross-

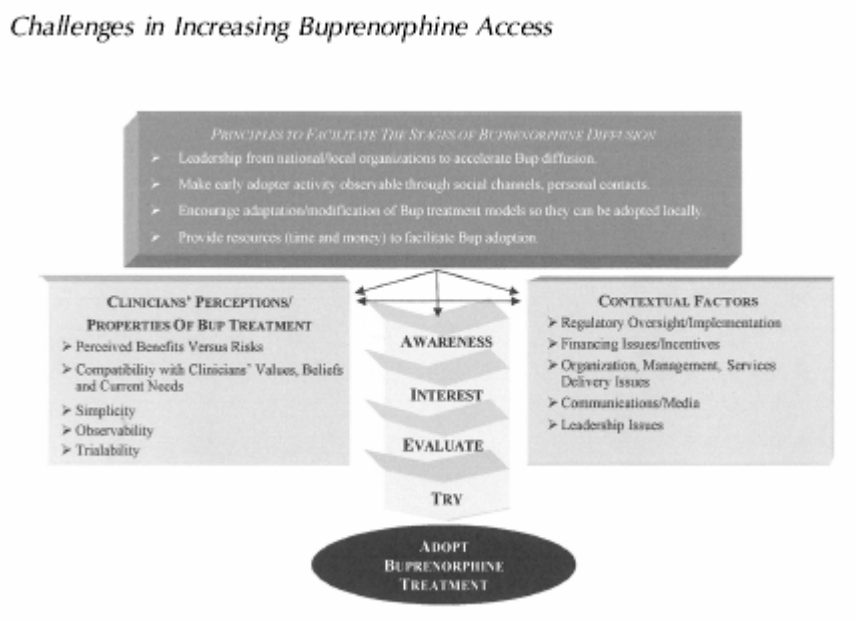
sectional and longitudinal analysis to study the clinical characteristcs and treatment outcomes of 96 patients entering a clinical trial of buprenorphine in a primary care clinic (PCC), compared to those of 94 patients receiving methadone maintenance in an opioid treatment program (OTP). They found that patients in the new-to-treatment PCC group were younger than their OTP counterparts who had received prior methadone treatment (36 versus 41 years), and were more likely to be white (77 versus 57 percent), to have a shorter history of opiate addiction (7 versus 14 years), to exhibit lower rates of injection drug use (35 versus 54 percent), and were less likely to have hepatitis C (25 versus 61 percent).

Significantly, abstinence and treatment retention rates were comparable in both groups. The investigators concluded that office-based treatment with buprenorphine is associated with new patients entering treatment (Sullivan, Chawarski et al., 2005).

Strategies to encourage more physicians to use buprenorphine in office-based treatment of addiction have been the subject of considerable attention. As in other areas of prescribing, current approaches focus on systematic barriers to change, aligning economic and non-economic incentives, and deploying information to clinicians and other decisionmakers (Naylor, 2004).

West, Kosten et al. (2004) devised a schematic (Figure 1) that identifies barriers to wider adoption of buprenorphine, which they identify as involving (1) perceived benefits versus risks, (2) compatibility with clinicians' values, beliefs and current needs, (3) simplicity, observability, and trialability.

Figure 1: Conceptual Model of Factors Affecting Adoption of Buprenorphine Treatment



SOURCE: West JC, Kosten TR, Wilk J et al. (2004). Challenges in increasing access to buprenorphine treatment for opiate addiction. *The American Journal on Addictions* 13:S8-S16 (page S14)

To overcome these barriers to physicians' use of buprenorphine – and, by extension, other new pharmacotherapies – Saxon and McCarty suggest a number of strategies, including:

- *Educational strategies:* More aggressive programs of physician and counselor training and mentorship; educational designs that employ small group interaction with active participation; educational outreach by experts or trained facilitators; (possibly) engagement of opinion leaders.
- *Substitution of professional tasks:* Engaging non-physician staff in assisting with some supportive and coordinative activities; expanding the role of pharmacists.
- *Organizational acceptance:* A focus on organizational acceptance, so as to engage a full range of systemic and environmental supports for practicing physicians.
- *Financial interventions:* Compensation on par with that for other treatments of similar complexity.

Krantz and Mehler (2004) endorsed similar strategies. Turner and colleagues (2005) added "access to an addiction expert" to the list of factors that might encourage greater engagement of primary care physicians. Raisch, Fudala et al. (2005) suggested outreach to pharmacists and pharmacy technicians.

International Experience. In most European countries, methadone treatment is provided to only 20 to 30 percent of persons who are addicted to opioids because of regulatory impediments and concerns about methadone safety (Auriacombe, Fatseas et al., 2004). To address the unmet treatment need, buprenorphine was approved for use in France in 1996. All registered physicians are allowed to prescribe buprenorphine without any special education or licensing. As a result, approximately 80,000 patients per year – half of all opiate addicts – are treated with buprenorphine (Feroni, Peretti-Watel et al., 2005b).

French compensation mechanisms, pharmacy services, and medical insurance funding all minimize the barriers to use of buprenorphine, with the result that one in five French physicians prescribes the drug. Auriacombe et al. (2004) and other observers have estimated that diversion and intravenous abuse of buprenorphine occur in 20 to 50 percent of buprenorphine maintenance patients, perhaps because the French use a version of buprenorphine without naloxone.

In the United Kingdom, where general practitioners play a pivotal role in the care of opiate-addicted patients (Strang, Sheridan et al., 2005), high-dose buprenorphine has been approved for the treatment of opiate addiction since December 1999. To examine buprenorphine's impact on the delivery of treatment services in the U.K., de Wet and colleagues examined data from 28 regional health authorities in England for the period September 2001 through September 2003. They found that prescriptions for buprenorphine increased in all 28 jurisdictions, from 47,000 in the 3rd quarter of 2003 to 125,000 in the 3rd quarter of 2003 (an increase of 166 percent). However, there was wide variation in buprenorphine prescribing among regions, which the author speculate may reflect differences in local experience and expertise, the complexity of the patient population, availability of resources for delivering maintenance and withdrawal. They further hypothesize that proportional rates of buprenorphine use may be highest in jurisdictions where there are strong linkages between specialist services and primary care physicians (de Wet, Reed et al., 2005). Similar results have been reported by Simoens, Matheson et al. (2005).

In Australia, high-dose buprenorphine maintenance treatment has been available since November 2000. The drug has found widespread use, particularly in the State of Victoria (capital: Melbourne), where early research trials were conducted. Australia has a more structured program for buprenorphine use than does France. Maintenance patients are required to attend a clinic or community pharmacy, where each dose is taken under supervision. National guidelines recommend that patients be observed for at least 3 to 7 minutes, or until the buprenorphine tablet has dissolved completely. Take-home doses are not routinely given (Jenkinson, Clark et al., 2005).

Summary. The literature evaluating the effects of the Waiver Program on availability of treatment for opiate addiction can be summarized as follows:

1. The availability of buprenorphine treatment under the Waiver Program appears to have engaged patients in treatment who were not part of the population being treated with methadone in OTPs.
2. There is no evidence that the availability of methadone treatment has decreased as a result of the introduction of buprenorphine.
3. Overall treatment capacity has expanded to some extent. Baseline data published by the buprenorphine post-marketing surveillance group will be useful in monitoring this situation in the future (Koch, Arfken et al., 2006).
4. Further engagement of primary care physicians in use of buprenorphine in office-based treatment of opiate addiction will require steps to overcome multiple impediments, such as physicians' inadequate knowledge of and negative attitudes toward addiction, financial disincentives, and lack of organizational supports.

FINDINGS: PUBLIC HEALTH CONSEQUENCES

The Evaluation of the Buprenorphine Waiver Program examined three key issues related to public health consequences. The first involves diversion and abuse of buprenorphine, where abuse was compared to rates of abuse of other prescription drugs, including methadone. The second involves adverse drug events and other negative health events associated with use of buprenorphine. The third involves the effects of buprenorphine treatment on risky personal and social behaviors.

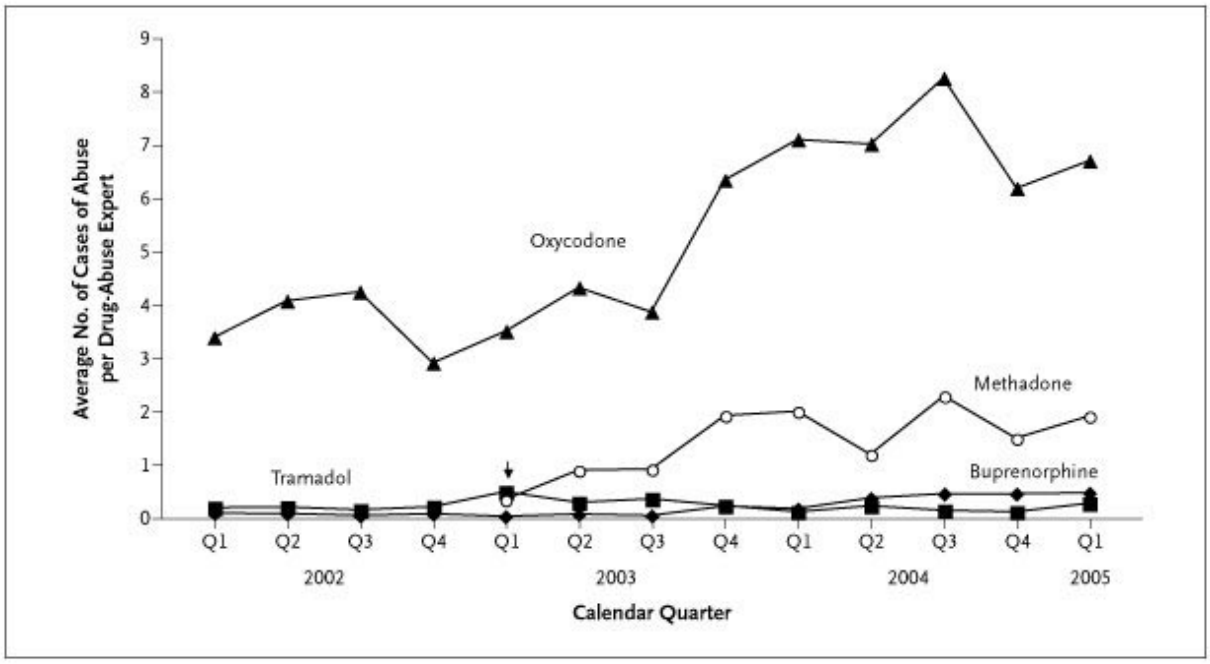
Diversion and Abuse. While early reports based on animal studies suggested that buprenorphine would have a low potential for abuse, varying levels of diversion and abuse were predicted by early investigators (Jaffe & O'Keeffe, 2003) and, in fact, have been reported worldwide wherever the drug has been used for addiction treatment and, to a more limited extent, in the management of pain (Jenkinson, Clark et al., 2005).

The most common pattern of abuse involves crushing the sublingual tablets and injecting the resulting extract (Cicero & Inciardi, 2005). When injected intravenously, addicts have described the clinical effects of buprenorphine as similar to equipotent doses of morphine and heroin (Sporer, 2004). Investigators also have found that intravenously administered buprenorphine serves as a reinforcer in recently detoxified, non-treatment-seeking heroin addicts. Moreover, under experimental conditions, buprenorphine was as effective as methadone in producing reinforcing and subjective effects. Based on follow-up interviews with study subjects,

researchers have hypothesized that, by suppressing withdrawal symptoms, the buprenorphine was acting as both a positive and negative reinforcer (by providing euphoric effects and alleviating withdrawal) (Comer, Sullivan et al., 2005a).

PREVALENCE: Established surveillance networks report that levels of buprenorphine abuse have remained essentially flat in the 3+ years since its introduction in the U.S. Using two well-established informant networks, Cicero and Inciardi (2005) reported that the level of buprenorphine abuse remained relatively low through the first quarter 2005 (and was roughly equal to rates of abuse of tramadol, an unscheduled analgesic). Moreover, abuse of buprenorphine appeared to occur at a level much lower than that seen with methadone or oxycodone (see Figure 2). The investigators added that the majority of buprenorphine abusers were young white males who had extensive histories of substance abuse. Significantly, more than a third of those users said they took buprenorphine in an effort to self-medicate or to ease the symptoms of heroin withdrawal. This is consistent with reports of "doctor-shopping" in France, where individuals engaged in efforts to obtain buprenorphine from multiple physicians were identified as receiving lower than recommended therapeutic doses of the drug (see the discussion, below).

Figure 2: Rates of Abuse of Buprenorphine, Tramadol, Methadone and Oxycodone, Compared



SOURCE: Cicero TJ & Inciardi JA (2005). Potential for abuse of buprenorphine in office-based treatment of opioid dependence. New England Journal of Medicine 353(17):1863-1865 (page 1864).

In a separate report of data gathered from the same key informant network, Cicero, Inciardi and Munoz (2005) ranked buprenorphine last in prevalence of abuse relative to the following drugs (listed here from highest to lowest prevalence of abuse): OxyContin, hydrocodone, other oxycodone, methadone, morphine, hydromorphone, fentanyl, and buprenorphine. For their

study, the authors examined populations of health care professionals (using data gathered from state programs for impaired practitioners), methadone patients, and pain patients for patterns of buprenorphine abuse. Health care professionals were of interest because they were among the earliest populations identified as abusing both pentazocine and fentanyl, they have ready access to prescription medications, and they are well aware of their euphorigenic properties. Methadone patients were of interest because they are seen as highly vulnerable to experimenting with all drugs, particularly opiates. Pain patients were included in the study because of the investigators' estimate that they were a high risk of iatrogenic addiction.

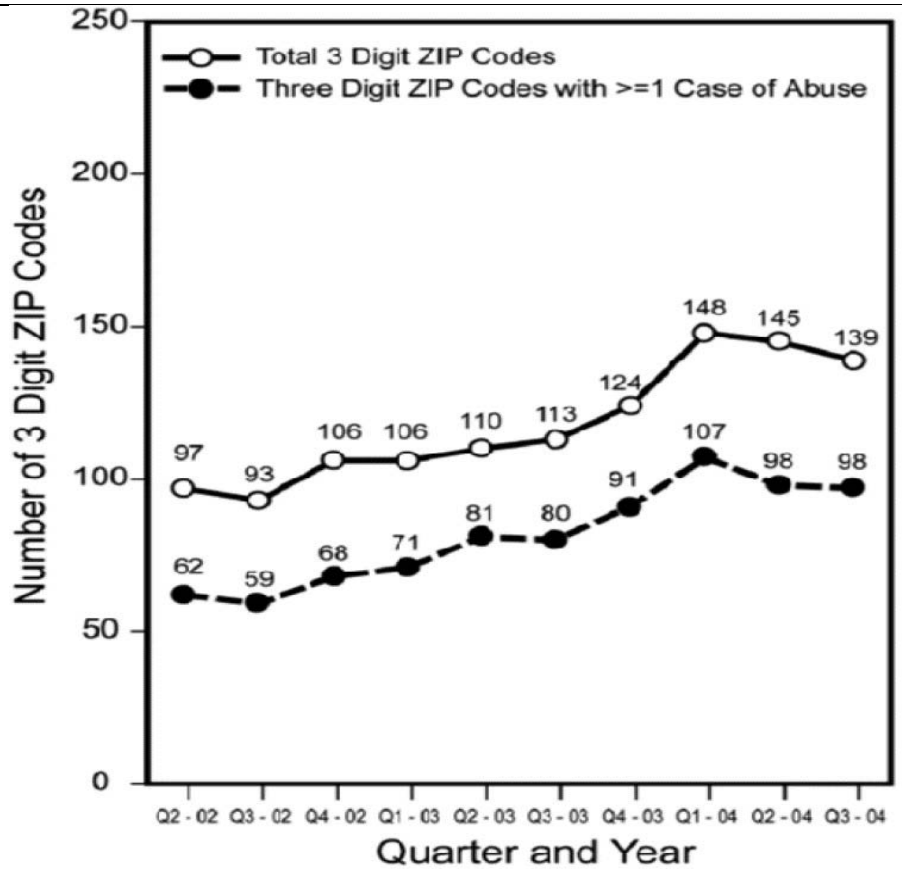
After mapping the three-digit Zip zones from which cases were reported in the years 2002, 2003, and the first three quarters of 2004, Cicero and colleagues concluded that abuse of prescription opiates was prevalent in all parts of the U.S., but seemed to be unevenly concentrated in the Eastern and Southeastern regions. Moreover, they hypothesized that such abuse tended to "migrate" from the Northeast and Appalachia to the Southeast and West, and that is appeared to be highly concentrated in rural, suburban, and small- to medium-sized cities. They noted its almost complete absence in large metropolitan areas in which heroin use is endemic (Cicero, Inciardi et al., 2005). Further, Cicero et al. concluded that the "sharp increase" in reports of buprenorphine abuse in the last 5 quarters of the study coincided with the introduction of Subutex and Suboxone (Figure 3).

While the actual number of Zip zones in which any abuse of buprenorphine was detected was very small – about 10 percent of all zip codes monitored – the investigators concluded that the increase in exposure resulting from availability of the new products led to an almost immediate increase in their non-medical use and abuse. They noted that this is not unusual, in that historical data show a period of experimentation following the introduction of many drugs (Cicero, Inciardi et al., 2005). Nevertheless, the identified trend requires continued monitoring.

SOURCES: Experts speculate that most buprenorphine obtained for non-medical purposes in the U.S. is diverted from prescriptions written for the treatment of addiction. In such instances, physicians may be careless, lack sufficient knowledge to prescribe appropriately, or lack the resources or will to monitor patients' progress post-prescription. Patients – driven by various motivations – also contribute through evasive and deceptive behaviors. For example, "doctor-shopping" (as when a patient consults multiple physicians to obtain prescriptions for a desired drug) has long been implicated as a method of diversion (AMA, 1981).

Another potential source is illegal importation. In addition to personal importation by individuals and large-scale smuggling rings, anecdotal reports and preliminary studies suggest that Internet pharmacies are a significant source of prescription medications obtained for use and misuse in the United States (Wilford, Smith et al., 2005). While the precise volume of Internet drug sales is not known, U.S. authorities have estimated that more than 20 million packages containing pharmaceuticals purchased online enter the U.S. each year. In a joint operation by the U.S. Customs Service and the FDA, agents seized a random sample of drug packages that arrived at international mail centers in seven U.S. cities and two commercial courier facilities. More than 80% of the parcels contained drug products that violated FDA regulations in some way: they were unapproved foreign drugs, or controlled substances, or counterfeits. Of the samples subjected to laboratory analysis, 14 percent contained no active ingredient at all (Grayson, 2004).

Figure 3: Number of Three-Digit Zip Zones Reporting Any Abuse of Buprenorphine, 2002-2004



SOURCE: Cicero TJ, Inciardi JA & Munoz A (2005). Trends in abuse of OxyContin and other opioid analgesics in the United States: 2002-2004. *The Journal of Pain* 6(10):662-672 (page 667).

In a 2004 White Paper on Internet Pharmacy, researchers at the national Center on Addiction and Substance Abuse at Columbia University reported that during a one-week period, they identified 495 Internet sites advertising controlled drugs. This included 338 "portal sites" that led to another site for purchase of the drugs, as well as 157 "anchor sites" that directly sold the advertised drugs. Forty-seven percent of the sites said that drugs would be shipped from outside the U.S.; 28 percent said the drugs would be shipped from within the U.S.; while 25 percent gave no indication of the origin of the drugs. Only six percent of the Internet sites said they required a prescription to complete a sales transaction and not a single site placed any restriction on the sale of the drugs to children (CASA, 2004).

While none of the studies to date has specifically identified buprenorphine in the list of drugs available, it is not improbable that it could be obtained via this route, in the same manner as other scheduled opiates such as Percodan® and Vicodin® (GAO, 2004).

INTERNATIONAL EXPERIENCE: International reports – particularly those from France and Australia – parallel (and predict) those on the U.S. experience with buprenorphine diversion and abuse.

To assess the degree to which buprenorphine was being diverted and abused in Melbourne, Australia, Jenkinson et al. (2005) designed a study in which 156 current injecting drug users participated in a 45-minute structured interview. Participants ranged in age from 18 to 52 years, and most (62 percent) were male. Unlike the findings in French studies, almost all the IDUs had stable living arrangements and only 3 percent were homeless at the time of interview.

Moreover, much of the diversion involved the buprenorphine/naloxone combination, rather than buprenorphine alone (Bell, Byron et al., 2005).

Fifty-seven percent of the study population reported using buprenorphine at least once in their lifetime. Of the 53 percent who said they had used buprenorphine in the preceding six months, a third said they had obtained it illicitly, often using drug prescribed for another. Injection of buprenorphine was highly associated with injection of other drugs – in fact, investigators found an almost linear correlation between the number of drug types injected in the preceding six months and the likelihood of injecting buprenorphine (Jenkinson, Clark et al., 2005). (The authors note that rates of injection reported in the Melbourne study were significantly higher than in other Australian jurisdictions, reflecting the disproportionate availability of buprenorphine in Melbourne.)

To assess rates of buprenorphine abuse in the United Kingdom, Schifano and colleagues used multiple official sources to gather data on buprenorphine prescriptions, seizures, and adverse events during the period 1980 to 2002 (their data include low-dose buprenorphine given as an analgesic). The investigators identified 43 fatalities in persons using buprenorphine, the majority of which occurred in the 1999-2002 time frame and involved concurrent use of benzodiazepines or other opiates. (By comparison, 167 deaths involving methadone were reported in the U.K. in the year 2003 alone [Luty, O'Gara et al., 2005].) In seven of the 43 buprenorphine-related deaths, confounding variables were ruled out by the investigating authorities and buprenorphine toxicity alone was reported as the cause of death (Schifano, Corkery et al., 2005), which the authors suggest raises questions about claims of buprenorphine's high safety profile.

Adverse Drug Events. Because it is a partial agonist, buprenorphine's effects plateau at higher doses, which limits both the maximal analgesic effect and respiratory depression (Gonzalez, Oliveto et al., 2004). However, norbuprenorphine – a product of N-dealkylation by the cytochrome P-450 3A4 enzyme, has more potent respiratory depressant effects than the parent drug. Drugs that induce 3A4 (such as phenobarbital, carbamazepine, and phenytoin) could increase norbuprenorphine levels, although the clinical effects of these interactions are unknown (Sporer, 2004).

Overdose deaths have been reported, most involving concurrent use of buprenorphine and CNS depressants such as benzodiazepines, other opiates, or alcohol (Sporer, 2004). An unknown number represent intentional drug overdoses (Tournier, Molimard et al., 2005). While the majority of decedents administered the drug intravenously, one death involving ingestion of a massive oral dose has been described (Drummer, 2005).

To evaluate the safety and ceiling effect of buprenorphine, Umbricht et al. (2004) administered buprenorphine to six non-dependent opiate abusers residing on a research unit. In separate sessions, they tested doses of 12 mg buprenorphine sublingual, escalating buprenorphine

intravenous (2, 4, 8, 12 and 16 mg), and both intravenous and sublingual placebo. Physiologic and subjective measures were collected for 72 hours following drug administration. They found that buprenorphine "minimally but significantly" increased systolic blood pressure, but that changes in heart rate and oxygen saturation were not significant. They also found that buprenorphine produced substantial, but variable, mood effects, and that side effects generally were mild. Thus, they concluded that buprenorphine appears to have a ceiling for cardiorespiratory and subjective effects and a high safety margin, even when administered intravenously.

INTERNATIONAL EXPERIENCE: In France, the number of deaths associated with buprenorphine appears to be declining (Emmanuelli & Desenclos, 2005). Nevertheless, at least 137 deaths have been reported in individuals using buprenorphine since the drug was introduced for the treatment of addiction. Most fatalities involved parenteral injection of the sublingual formulation, almost always in association with other drugs, in the following frequency: benzodiazepines (78 percent), cannabis (50 percent), neuroleptics (32 percent), alcohol (29 percent), other psychotropics (21 percent), and other opiates (21 percent). However, only one of the 137 deaths did not have another possible explanation, raising a question as to whether buprenorphine had a causal role, was one of several contributing factors, or was merely present in the decedent's system (Auriacombe, Fatseas et al., 2004).

In the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), where a collaborative study of fatal poisonings among drug-addicted persons was undertaken by public health and forensic officials, buprenorphine was found to be associated with 16 of 94 overdose deaths reported in Finland in the study years (1991, 1997 and 2002), whereas only one death attributed to buprenorphine overdose was reported in the other four countries in those years. The disparity may be at least partially explained by the fact that all deaths are screened for buprenorphine in Finland, but only cases in which buprenorphine use is suspected are screened in the other countries, where reports of heroin- and methadone-related deaths predominate (Steentoft, Teige et al., 2005).

Reports of other adverse health events associated with buprenorphine include diffuse cystic leukoenchephalopathy (Seet, Rathakrishnan et al., 2005), abscess (Loo, Yam et al., 2005), necrosis (Feeney & Fairweather, 2003), fungal endophthalmitis (Albotins, Allen et al., 2005), and spondylodiscitis (Etchepare, Coutaux et al., 2005) – all in injecting drug users. Cazorla and colleagues (2005) found 21 cases of infections related to intravenous buprenorphine in one French university hospital between 1998 and 2003. The cases involved infectious endocarditis (9 cases), cutaneous abscesses (8 cases), osteoarticular infections (2 cases), and one case each of meningitis and Candida retinitis. A national evaluation of pharmacotherapies for opiate addiction in Australia involving more than 1,200 patients found no significant difference in rates of serious adverse events between methadone, LAAM, and buprenorphine, or between different doses of buprenorphine (Digiusto, Shakeshaft et al., 2004). A study in Germany, using the transdermal buprenorphine patch marketed for pain relief, found adverse events in 22 percent of the 13,179 patients evaluated. However, adverse reactions attributable to the buprenorphine itself were found in only 10 percent of the subjects (1,330 patients) (Griessinger, Sittl et al., 2005).

In India, where buprenorphine became available for the treatment of opiate addiction in 1999, researchers at the National Drug Dependence Treatment Centre (New Delhi) mounted a post-

marketing surveillance study involving 5,551 reports from 10 reporting addiction treatment programs. Most of the subjects were young adults. Of the 5,551 reports, 12 were judged to be significant adverse events, involving seizures, dyspnea, and fever. No cardiovascular or hepatic problems were found, and no deaths were reported. Analysis disclosed a significant correlation between duration, time since administration, and total subjective symptoms reported. The researchers found no correlation between dose and subjective symptoms (Ray, Hemraj et al., 2004).

Reduction in Risky Behaviors. An area of major interest is the effectiveness of buprenorphine in reducing risk behaviors for HIV (e.g., frequency of injection drug use, sharing of injection equipment, high-risk sexual behaviors, overall HIV risk, or rates of seroconversion). Sullivan and Fiellin (2005) reviewed the literature and reported that at least 13 randomized studies and clinical trials have documented buprenorphine's ability to reduce opiate use among injection drug users. However, they found few studies that documented changes in other risk behaviors or rates of seroconversion. One randomized trial showed a significant reduction in HIV risk behaviors from baseline to the end of the maintenance phase in patients receiving buprenorphine daily or 2 or 3 times a week. The authors concluded that more research is needed (as through the ongoing international HIV Prevention Trials Network) to clarify buprenorphine's effect on behaviors that place individuals at risk for HIV.

INTERNATIONAL EXPERIENCE: Results of the Australian Treatment Outcome Study (ATOS) suggest that buprenorphine may be as effective as methadone in producing reductions in risk behaviors such as continued drug use, criminal activity, and injection drug use (Teesson, Ross et al., 2005).

A German study comparing quality of life in 53 individuals treated for opiate addiction with either buprenorphine or methadone maintenance treatment (25 of whom could be located after three years) found clear benefits of buprenorphine therapy in terms of quality of life and health status, as well as a reduction in risk behaviors such as continued use of benzodiazepines (Giacomuzzi, Ertl et al., 2005).

In Norway, methadone was approved for the treatment of opiate addiction in 1998, buprenorphine in 2000. To compare the relative efficacy of the two maintenance therapies, Kristensen and colleagues (2005) randomly selected 25 patients receiving methadone and 25 receiving buprenorphine (both groups received other rehabilitation services as well). They found that, at 180 days, only the patients receiving buprenorphine reported significant improvements in their physical health. However, treatment retention was higher in the methadone maintenance group, the patients receiving methadone also had fewer urine tests that were positive for opiates, and they reported fewer risky behaviors.

Summary. The literature assessing the public health impact of the Buprenorphine Waiver Program generally shows:

1. There is a small but significant level of diversion and abuse of buprenorphine, with a trend line that appears essentially flat. This is consistent with the pattern seen with other prescription opiates, and with the predictions of experts who testified in favor of the drug's approval for the treatment of opiate addiction. Unlike other opiates, however, the

trend line for prevalence of buprenorphine abuse has remained essentially flat from the time it was introduced in 2002 to the present.
2. Some level of "doctor-shopping" and other forms of diversion may represent efforts at self-medication rather than intentional abuse (e.g., involving patients whose physicians prescribe less than the recommended therapeutic dose of buprenorphine).
3. While adverse drug events have been reported, most are associated with injection of the crushed sublingual tablets, rather than use of the drug as prescribed.
4. Buprenorphine maintenance therapy appears to contribute to reduction in some behaviors associated with HIV risk, but the overall picture is not yet clear.

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