Published in final edited form as:
Curr Drug Abuse Rev. 2011 March 1; 4(1): 28–41.

Buprenorphine and Buprenorphine/Naloxone Diversion, Misuse, and Illicit Use: An International Review

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Abstract

The diversion, misuse, and non-medically supervised use of buprenorphine and buprenorphine/naloxone by opioid users are reviewed. Buprenorphine and buprenorphine/naloxone are used globally as opioid analgesics and in the treatment of opioid dependency. Diversion of buprenorphine and buprenorphine/naloxone represents a complex medical and social issue, and has been widely documented in various geographical regions throughout the world.

We first discuss the clinical properties of buprenorphine and its abuse potential. Second, we discuss its diversion and illicit use on an international level, as well as motivations for those activities. Third, we examine the medical risks and benefits of buprenorphine's non-medically supervised use and misuse. These risks and benefits include the effect of buprenorphine's use on HIV risk and the risk of its concomitant use with other medications and drugs of abuse. Finally, we discuss the implications of diversion, misuse, and non-medically supervised use (including potential measures to address issues of diversion); and potential areas for further research.

Keywords

Buprenorphine; buprenorphine/naloxone; diversion; injection drug use; self treatment; Suboxone; Subutex; opioid dependence; opioid abuse; opiate abuse; opiate dependence

INTRODUCTION

Opioid Dependence: Extent of the Problem

Opioid abuse and dependence are major medical and social concerns throughout the world, contributing to excessive morbidity, mortality, disability, and economic costs [1, 2]. The United Nations Office on Drugs and Crime notes that opiates, particularly heroin, are the main problem drugs at a global level, with an estimated 15.6 million opioid abusers globally, including approximately 11.1 million heroin abusers [3]. The WHO also estimates that there are approximately 12.6 million injection drug users (IDUs) in the world [4], with injection drug use reported in over 150 countries and territories globally [5]. While the prevalence of

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

injection drug use may be low in any given general population, IDUs represent a major point of entry for HIV into a population; according to UNAIDS, injection drug use accounts for up to 80% of HIV infections in Eastern Europe and Central Asia [6].

In addition to the risk of HIV infection and transmission, other harms associated with injection drug use present additional medical challenges. Unsafe injection practices have contributed to an international epidemic of Hepatitis C virus, with an estimated 120 million people infected worldwide [7]. Abscesses, endocarditis, and soft tissue infections are prominent concerns for the health of IDUs [8–10]. Finally, regular use of opioids, regardless of the route of administration, results in lasting biological and physiological changes in the brain, including disruptions in inhibitions, motivation, and decision-making processes [11].

Opioid replacement therapy with methadone or buprenorphine is a clinically effective treatment for opioid dependence. Methadone was first used to treat opioid dependence in the 1960's [12]. It is a synthetic full mu-receptor agonist that is usually administered to patients orally on a daily basis for opioid replacement [13]. Buprenorphine, which is described in greater detail below, is a partial mu-agonist that is administered sublingually to patients undergoing opioid substitution therapy [13]. Studies examining the effectiveness of opioid substitution treatment have found that it results in superior retention rates (in comparison to abstinence only treatment) [14], reduces the amount of illict and nonprescribed opioids used by patients [12, 14–16], decreases criminal activity [14, 17], and helps to reduce the transmission of HIV among drug users and the occurrence of high-risk injection practices [14, 17–19].

While the ultimate goal of substance abuse treatment is abstinence, opioid addiction is a chronic, relapsing medical condition. In this article, we take a harm reduction approach to analyze the use of buprenorphine and buprenorphine/naloxone by opioid users.

Buprenorphine - Course of Action, Safety, and Clinical Efficacy

Buprenorphine is a relatively long-acting partial mu agonist and full kappa antagonist administered sublingually in opioid replacement therapy [13, 20, 21]. Buprenorphine is commonly sold alone (Subutex®) or in a coformulation with naloxone (Suboxone®) to prevent parenteral abuse [13, 22–25]. As a partial agonist, buprenorphine exhibits a ceiling effect at high doses. This means that there is a plateau observed for buprenorphine's opioid agonist effects, such as sedation and respiratory depression, even at high doses. In experimental settings, doses up to 70 times the recommended analgesic dose were well tolerated in non-dependent males who had previous experience with opioids [20].

Buprenorphine was first used at low doses as an analgesic for post-operative and cancer patients in the late 1970s [26, 27]. Shortly thereafter, reports of buprenorphine misuse—marketed at the time as Tamgesic®—began to surface in New Zealand [28] and reports of injection misuse arose in Europe [29]. A recent report from the World Health Organization Expert Committee on Drug Dependence noted that, while diversion is currently occurring and does pose a public health concern, the risk-to-benefit ratio for the continued use of buprenorphine is favorable [30].

High-dose buprenorphine—available in 0.4mg, 2.0mg, and 8.0mg doses—was introduced in 1980 for the treatment of opioid dependency [31–33]. Buprenorphine is a well-suited medication for opioid replacement therapy due to its activity as a partial opioid agonist. Buprenorphine can be substituted for full agonists, such as heroin or morphine, to prevent withdrawal but it can also be slowly withdrawn without large discomfort, as is often experienced with methadone [34].

Numerous trials and reviews have established buprenorphine as an effective treatment for opioid dependence. Buprenorphine is safe and effective for use in acute detoxification, stabilization, and long-term maintenance of individuals with opioid dependence. In a randomized controlled trial of buprenorphine, Johnson and colleagues found that buprenorphine was effective in maintaining patients in treatment and reducing the consumption of illicit opioids [35]. Additional studies have shown that office-based treatment (OBT) with buprenorphine is effective and safe for the treatment of opioid dependency [36, 37]. Office-based therapy provides additional benefits, including minimization of contact with other drug users and of the stigma associated with drug dependence [21, 38]. As a result of buprenorphine and buprenorphine/naloxone's safety profiles, the U.S. National Institute on Drug Abuse has identified the medication as a first-line treatment for opioid dependence [39]. The WHO also added buprenorphine as a complementary medication to the 14th edition of The Model of List of Essential Medicines [4].

Buprenorphine is intended for sublingual administration. Due to extensive first-pass liver metabolism, oral dosing of buprenorphine results in low bioavailability and is not feasible. With sublingual administration, the medication achieves sufficient bioavailability after being dissolved under the tongue, usually within 5–7 minutes of administration. Buprenorphine/naloxone is also intended for sublingual dosing, and while the sublingual bioavailability of buprenorphine is relatively high (ca. 35–55%), that of naloxone is low (ca. 10%); this property allows the combination buprenorphine/naloxone product to deliver the effects of the opioid without those of the antagonist, when used as directed [24, 40, 41]. If buprenorphine/naloxone is injected, however, the bioavailability of naloxone is high; in such an instance, the naloxone component is intended to both precipitate withdrawal and block the euphoric/analgesic effects of buprenorphine in opioid-dependent individuals [25]. However, at the current 4:1 buprenorphine/naloxone coformulation ratio, the naloxone component does not significantly reduce the effects of buprenorphine when the combination product is injected by individuals who are not dependent on opioids [42]. Thus, buprenorphine/naloxone is intended to reduce the risk of abuse *via* injection [22–25].

Although the analgesic properties of buprenorphine and its potential indication for pain management were documented as early as the 1970's, new research has examined buprenorphine's role in chronic pain management, post-operative pain management, and non-cancer pain management. In particular, the efficacy and safety of transdermal buprenorphine has been studied with positive results. Transdermal buprenorphine was studied with chronic osteoarthritis patients, demonstrating good efficacy and tolerability [43], and was also studied in a randomized controlled trial for chronic low back pain, where it was effective at managing pain in patients who had previously received opioids [44]. The use of sublingual buprenorphine for pain management has also been studied, with the medication showing a high degree of efficacy, tolerability, and safety in patients with chronic pain syndrome, even in individuals who suffer from opioid addiction [45]. In a double-blind comparison of sublingual and transdermal buprenorphine in patients with osteoarthritis pain, both forms showed similar efficacy, and transdermal buprenorphine demonstrated better tolerability among patients [46]. Although buprenorphine has not been extensively used in clinical practice for pain management, current evidence suggests that buprenorphine may be well-suited for pain management, particularly in high-risk patients, such as diabetics, the elderly, or individuals with renal failure, due to buprenorphine's good safety profile, ceiling effect on respiratory depression, low incidence of adverse events, and pharmacokinetics that are unaltered by age or renal function [47].

Buprenorphine is currently used in dozens of countries throughout the world for the treatment opioid dependence and, in some instances, for pain management. Dosing policies,

access to treatment, levels of patient supervision, and government policies vary widely among individual countries.

Since 1995, all primary care physicians in France have been able to prescribe buprenorphine to patients suffering from opioid dependence. Physicians in France are not required to undergo any specific training to prescribe buprenorphine and do not have any limits on the number of patients who may receive buprenorphine [48]. In that country, HIV prevalence and rates of fatal opioid overdose among IDUs have dropped significantly since the widespread introduction of buprenorphine [31]. By 2006, approximately 95,000 patients were receiving buprenorphine for the treatment of opioid dependence in France [49].

The United States was the first country to widely use combination buprenorphine/naloxone (Suboxone®) for office-based treatment (OBT) of opioid dependence. Under provisions of the US Drug Abuse Treatment Act of 2000 (DATA 2000), any physician can undergo a training course and subsequently apply for a license to prescribe buprenorphine/naloxone to individuals with opioid dependence on an out-patient basis [48]. Each physician is initially limited to 30 patients, but can later apply to prescribe buprenorphine/naloxone to a maximum of 100 patients [48].

Buprenorphine was approved in Australia in 2000 for detoxification and maintenance of opioid-dependent patients [50, 51]. Patients commonly receive their dose of buprenorphine in a pharmacy or community clinic, where the pharmacist or a staff member directly administers the medication on-site, usually waiting 3–5 minutes before staff inspect the patient's oral cavity [52]. Buprenorphine/naloxone (Suboxone®) was approved for the treatment of opioid dependence in 2005 [51].

Buprenorphine was first introduced in India in 1986 as an analgesic (Tidigesic®), and reports of buprenorphine ampoule abuse were reported shortly thereafter [53]. Buprenorphine was approved for the treatment of opioid dependence in India in 1999 [54]. In Malaysia, buprenorphine was first licensed for prescription in 2003, and was not highly regulated. Consequently, reports of abuse quickly emerged and, in 2006, buprenorphine/naloxone was introduced to replace buprenorphine in the Malaysian market with the aim of decreasing the practice of buprenorphine injection [55].

Abuse Potential of Buprenorphine

Several studies have examined the reinforcing effects and abuse potential of buprenorphine. Buprenorphine administration in non-opioid dependent individuals produces the euphoric effects typically associated with opioids [56, 57]. Subsequent research has demonstrated that buprenorphine does exhibit positive-reinforcement properties, similar to other opioids [58–60]. For example, in a study conducted by Comer *et al*., participants received a dose of buprenorphine, buprenorphine/naloxone, or placebo and $20, and were subsequently allowed to choose between a dose or $20 in a choice session; those who received the actual medication were more likely to self-administer another dose in comparison to those receiving the placebo [58]. Another evaluation of buprenorphine in detoxified males with heroin dependence produced significant euphoria in the participants, but the abuse liability was considered moderate in comparison to morphine [61]. The abuse potential for buprenorphine is generally considered to be less than that of full opioid agonists [62, 63]. Collectively, these data indicate that there is some cause for concern regarding initiation of opioid misuse with buprenorphine, although this risk is lower than that of most other opioids.

In opioid-dependent individuals, sublingual or parenteral administration of buprenorphine may precipitate withdrawal and/or limit the reinforcing effect of full agonist opioids, due to

its properties as a high-affinity partial agonist [30, 64–68]. Therefore, due to buprenorphine's mixed agonist-antagonist properties, several studies have concluded that the risk of buprenorphine abuse among opioid-dependent individuals is relatively low [31, 58, 69].

A direct comparison of the prevalence of buprenorphine and buprenorphine/naloxone abuse is difficult, since each product was introduced into different locations at different times. For example, in the United States, the monoproduct was never extensively used before the introduction of the combination product, and heroin remains cheap and highly accessible on the street. As a result, buprenorphine is not a major drug of abuse in the US. On the contrary, in many European and Asian countries, buprenorphine monoproduct was available for years before the introduction of the coformulated product, and limited heroin availability may have prompted IDUs to make buprenorphine their primary drug, especially in regions where buprenorphine was not highly regulated. Thus, the overall prevalence of buprenorphine or buprenorphine/naloxone abuse is not simply a function of the biological properties of these medications, but rather is dependent on a variety of social, cultural, political, and economic forces.

BUPRENORPHINE DIVERSION AND ILLICIT USE

Diversion and Illicit Use of Buprenorphine

Buprenorphine abuse by injection was first recorded in the mid-1980s [28, 29]. In the last two-and-a-half decades, buprenorphine diversion and illicit use have been documented in countries around the world. In some countries, such as Finland, buprenorphine is the most widely abused opioid, whereas its abuse in other nations exists to a much lesser extent. Regardless of the location, various studies, which will be explored further in this section, have identified motivations for illicit use and abuse. Table 1 displays information from a selection of relevant studies examining buprenorphine diversion from various geographical locations. The studies displayed in Table 1 represent articles on buprenorphine diversion that were published within the last 10 years. The goal of this table is not to be an exhaustive list of studies; instead it illustrates the range of geographic locations where buprenorphine diversion has been noted, along with relevant findings to demonstrate the range of diversion levels in diverse geographical settings.

Since buprenorphine's widespread introduction in France for the treatment of opioid dependence in 1995, illicit use and misuse of buprenorphine have been widely documented. One study reported up to 20% of buprenorphine patients were misusing their prescription intravenously [31] (see Table 1). Another French study found that 27% of IDUs were exclusive buprenorphine injectors, with another 37% reporting polydrug use [70]; some of these IDUs may have purchased their buprenorphine from individuals with a prescription [71], while others may have obtained buprenorphine by altering or forging prescriptions [63, 72, 73]. Obadia *et al*. reported similar findings, with 24% of their IDU sample reporting exclusive buprenorphine use and 34% reporting polydrug use with buprenorphine [74]. While injection of buprenorphine remains the most commonly reported route of administration for misuse of the medication, sniffing has also been reported in France [75] and elsewhere [76].

In Finland, buprenorphine, which has been used for pain management since 1997 and was introduced in 2002 for the treatment of opioid dependence, is the most commonly abused drug by IDUs and the most commonly abused opioid [77, 78]. A sharp increase in the misuse of buprenorphine coincided with a notable decrease in 2001 in the availability of heroin in Finland [77]. Among those entering treatment for opioid dependence, Aalto *et al*. found that 29 of 30 patients (97%) reported buprenorphine as their primary drug of abuse

[77]. Among a larger sample of syringe exchange program (SEP) participants in Finland (n=176), buprenorphine was the most frequently abused injection drug (73% of respondents), yet a significant portion of these individuals reported using buprenorphine in a therapeutic manner, to self-treat withdrawal or addiction [79] (see Table 1). Elsewhere in Europe, illicit buprenorphine use has been reported in Sweden [80], Scotland [81, 82], Norway [83], Ireland [84], and Spain [85].

Numerous studies have examined the issue of misuse and non-medically supervised use of buprenorphine in Australia, where the medication is strictly regulated. Buprenorphine was introduced in Australia in 2000, followed by the introduction of buprenorphine/naloxone in 2006 in response to concerns of buprenorphine diversion and illicit use [86]. In two separate studies, about 1/3 of IDUs reported recent buprenorphine injection [87, 88] (see Table 1); however, buprenorphine was the primary drug of abuse in only about 10% of IDUs [87]. A significant proportion of primary buprenorphine injectors had a prescription for the medication [87]. In a cross-sectional study of clients receiving buprenorphine in public clinics, about one-quarter (26.5%) had ever injected buprenorphine and most patients reported wanting to take their medication as prescribed [50] (see Table 1). Buprenorphine diversion by patients receiving supervised dosing at pharmacies has also been reported in Australia, which often occurs when patients remove the tablet before it is fully dissolved [89, 90]. In a recent study with 440 patients receiving opioid substitution therapy (methadone, buprenorphine, or buprenorphine/naloxone), Horyniak and colleagues found that 18% of their Australian participants ever inhaled buprenorphine or buprenorphine/naloxone, with smoking being the most common form of inhalation, while rates of buprenorphine and buprenorphine/naloxone snorting were relatively low. While lifetime rates of inhalation were relatively high, rates of recent inhalation were low. The authors postulated that these rates may indicate experimentation and not chronic use, and also propose that inhalation may represent a harm reduction approach to reduce the use of injectable opioids [86].

In the United States, buprenorphine was approved for analgesic use (Buprenex®) in 1985 as a Schedule V Medication. Buprenrophine (Subutex®) and buprenorphine/naloxone (Suboxone®) were introduced for office-based treatment of opioid dependence in 2002 as Schedule III Medications [91]. Buprenorphine/naloxone is a first-line option for office-based treatment, with the buprenorphine monoproduct used occasionally for the induction phase [92, 93]. The SAMHSA (Substance Abuse Mental Health Services Administration) Consensus Panel on Buprenorphine recommends that buprenorphine/naloxone be used for the induction, stabilization, and maintenance of most patients in the United States [94]. Currently, approximately 15,700 physicians can prescribe buprenorphine for the treatment of opioid dependence, with an estimated 3.5M prescriptions written for buprenorphine or buprenorphine/naloxone in 2008 [91]. Low levels of abuse have been detected since the medications' introduction, with buprenorphine and buprenorphine/naloxone generally ranked as the least-abused or misused opioid among those studied (examples of other opioids with higher rates of abuse in the U.S. include heroin, oxycodone, hydrocodone, methadone, morphine, and fentanyl) [95–99]. Buprenorphine/naloxone diversion has been limited and illicit buprenorphine/naloxone—which is frequently acquired from individuals with prescriptions—is commonly used in a therapeutic, non-medically supervised manner [33, 100, 101] (see Table 1).

In 2006, the Malaysian government replaced buprenorphine, which was introduced in 2001 [102], with buprenorphine/naloxone to address concerns of buprenorphine misuse and injection [55]. After the transition to buprenorphine/naloxone, there was no reduction in injection risk behaviors among IDUs, but an increase in their use of benzodiazepines [55] (see Table 1). The concomitant use of benzodiazepines has been identified elsewhere, and

has been attributed to an increase in euphoric effects of buprenorphine [53], although further investigation into the exact motivations for the concomitant use of buprenorphine and benzodiazepines is warranted. In some areas, benzodiazepines may be available over-the-counter, which may increase rates of concomitant use with buprenorphine. Despite reported withdrawal symptoms, IDUs did not decrease their self-administration of buprenorphine/naloxone [55]. In another Malaysian study, a large majority of buprenorphine IDUs reported lifetime (ca 100%) or current (ca 63%) heroin use [64] and many buprenorphine/naloxone injectors had developed methods to avoid the effects of naloxone, which included dividing the tablets into small pieces or mixing it with heroin or benzodiazepines [64]. Reports of buprenorphine abuse in India indicate that the use of street-acquired buprenorphine is common among heroin injectors [103]. Recent studies identified buprenorphine as the second most commonly injected drug (after heroin) in India, and also raised concern over the number of new IDUs who initiate injection with buprenorphine [104].

MOTIVATIONS FOR BUPRENORPHINE DIVERSION AND INJECTION

Motivations for Buprenorphine Injection

While the practice of diverting buprenorphine has been established in many regions throughout the world, few studies have examined the motivating factors for such diversion. Several publications, which are explored below, have identified price, withdrawal management, insufficient dosing, a lack of other drugs, and a pursuit of euphoria as possible motivations.

Price—In some regions, buprenorphine is cheaper than heroin when obtained legitimately for pharmacotherapy or when illicitly purchased on the streets [87]. In some instances, rising prices of other injectables may influence a transition to buprenorphine [33, 105, 106] or the lower price of buprenorphine may appeal to injectors who have limited income [84]. Additionally, the decision to inject buprenorphine may also be influenced by cost, as smaller doses can be used in comparison to sublingual dosing [64, 107]. Indeed, injection use of buprenorphine is the most biologically efficient route of administration (in terms of bioavailability) [108–111], with smaller IV doses required to obtain euphoric effects in comparison to other routes of administration. Although this efficiency may initially appear more economical, an individual who injects buprenorphine will quickly develop a level of tolerance that could ultimately result in greater consumption of buprenorphine.

Depending on the geographic region and the degree of availability of illicit buprenorphine, the medication may be significantly less expensive than comparable doses of other opioids. In other cases, heroin may be adulterated or hard to acquire. All of these conditions may contribute to the acquisition and use of illicit buprenorphine [84, 87, 105, 106, 112].

Euphoria—In any area with accessible buprenorphine, some level of diversion and abuse is to be expected, as is the case with all opioid medications. In various studies, rates of euphoria seeking, or using buprenorphine to “get high” range from 10% in some regions of Australia to 97% in Finland [79, 87] (see Table 1). As illustrated by the “Diversion and Illicit Use of Buprenorphine” section of this article, buprenorphine abuse rates vary widely across different geographic regions.

Illict Use as a Response to Sub-Optimal Clincial Dosing or Due to a Lack of Other Drugs—In some instances, patient misuse of buprenorphine by injection or inhalation may be indicative of sub-optimal clinical dosing [74, 75, 113]. In such cases, patients may not be receiving an adequate dose of buprenorphine, may be attempting to maintain the clinical effects of buprenorphine while using less medication (for instance, due to financial constraints), or may be diverting some of their medication to others (for

therapeutic purposes or for misuse) while still attempting to maintain buprenorphine's therapeutic effects.

Other Motivations for Buprenorphine Diversion

Studies examining buprenorphine diversion and illicit use have identified additional motivations for such behavior. In Singapore, for example, Chong *et al*. note that there is a false belief among IDUs that intravenous administration of buprenorphine can enhance erection [107]. In India, where buprenorphine was introduced as an ampoule analgesic in 1986, one study found that buprenorphine users, who constitute about 30% of all IDUs [104], were less likely to face threats of arrest in comparison to heroin users, that buprenorphine users believed they were less likely to be harassed by the police if they possessed buprenorphine rather than heroin, and that buprenorphine users generally only had minor histories of arrest and incarceration [114] (see Table 1). In another Indian study, an association was found between intensified police presence and increased injection of buprenorphine in comparison to the injection of heroin [106]. Collectively, these data indicate that law enforcement efforts may influence the drug use profiles of a population and may inadvertently encourage drug-dependent individuals to utilize forms of drugs that outwardly appear less illegal. Additionally, police enforcement in a particular area may affect the availability of particular forms of opioids, which could prompt opioid-dependent individuals to switch to other opioids that have greater local availability.

MEDICAL RISKS AND BENEFITS OF NON-MEDICALLY SUPERVISED BUPRENORPHINE USE

Medical Benefits of Non-Medically Supervised Buprenorphine Use

While there are public health, medical, social, and legal concerns regarding the misuse and illicit of buprenorphine, studies have identified various benefits of illicit buprenorphine use. In many instances, individuals using illicit buprenorphine may be doing so in an attempt to decrease the illicit use of other opioids, to self-treat opioid dependence, to manage or mitigate withdrawal symptoms [33, 80, 100, 108], or to attempt to reduce the level of harm associated with injection drug use [114] (see Table 1). Similarly, studies that examined differences between buprenorphine and non-buprenorphine IDUs have noted safer injection practices and lower rates of high-risk HIV activity among buprenorphine injectors [114, 115].

For example, in a recent study in the Republic of Georgia, where buprenorphine is an unregistered medication, only 13% of IDUs recruited from a needle exchange reported that buprenorphine was their drug of choice, while 42% reported using buprenorphine to cope with withdrawal symptoms and 6% used buprenorphine to stop using other drugs [116].

In the United States, a study examining entrants to office-based opioid treatment reported that a large majority of patients had used non-medically supervised buprenorphine to prevent cravings and to prevent the onset of withdrawal symptoms [33] (see Table 1). In a qualitative study in Massachusetts and Vermont, treatment seekers also frequently reported using illicit buprenorphine and similar results were found, with patients indicating non-medically supervised buprenorphine use to prevent withdrawal and to self-treat withdrawal symptoms [100]. A 2009 U.S. study examining the use of illicit buprenorphine among out-of-treatment injection and non-injection drug users found that a majority of participants used the medication to reduce opioid withdrawal symptoms and to self-treat opioid addiction, with more IDUs than non-IDUs reporting buprenorphine use for these purposes. That same study also noted that about three quarters of IDUs and half of non-IDUs used diverted

buprenorphine because they could not afford to enter formal drug treatment [101] (see Table 1).

Additional data from Hakansson *et al*. reported in 2007 showed that a majority of surveyed heroin users (89%) in Sweden reported buprenorphine use in their lifetime, and that among those illicit users, 87% were using buprenorphine therapeutically, for self-detoxification or withdrawal treatment. In that same study, sublingual administration of illicit buprenorphine was most common, consistent with the medication's intended mode of administration [80].

In Malaysia, Bruce *et al*. found that injectors were using diverted buprenorphine as a treatment modality, frequently reporting non-medically supervised buprenorphine use to avoid heroin or morphine withdrawal. Participants also reported subjective improvements in quality of life after transitioning to buprenorphine. Buprenorphine use often allowed these users to obtain and sustain employment, which they were unable to do while injecting heroin [108].

HIV Risk Behavior and Illicit Buprenorphine

Few studies have examined the associations between non-medically supervised buprenorphine use and HIV risk behavior. Sullivan *et al*. found that office-based buprenorphine treatment in the U.S. was associated with decreased drug-related HIV risk behavior, including decreased injection drug use and decreased needle sharing among in-treatment participants [115]. It is possible that non-medically supervised buprenorphine users experience similar benefits. In India, Kumar *et al*. noted that illicit buprenorphine injectors were less likely to share injection equipment and had fewer drug using members in their social networks [114], which could potentially have a significant impact on injection drug-related risk of HIV infection. Likewise, in France, individuals who exclusively inject buprenorphine reported lower rates of needle sharing and polydrug use, while simultaneously having higher rates of employment in comparison to heroin or cocaine injectors [31]. Higher rates of employment among exclusive buprenorphine injectors may indicate that buprenorphine injectors have more stable living situations, possibly due to a lower severity of addiction, than their heroin- and cocaine-injecting counterparts. What is not known is whether this is a function of the drug itself or of the type of drug user who uses buprenorphine by injection.

Medical Risks of Illicit Buprenorphine Use

Despite the therapeutic benefits of non-medically supervised buprenorphine use, concerns regarding the misuse of diverted buprenorphine, particularly when administered *via* injection, should also be considered. Adverse events associated with buprenorphine injection are similar to those of other injected substances. There have been several reports of abscesses, soft tissue infections, emboli, acute limb ischaemia, endocarditis, sepsis, and HIV and Hepatitis C infection associated with injection of buprenorphine [9, 31, 107, 117, 118]. Also, in areas where supervised sublingual dosing of buprenorphine occurs, subsequent injection of the partially dissolved medication may pose a high risk of microbiological contamination [87], as microbial flora from a patient's mouth may be present on the tablet that will later be injected.

Another concern that arises with the diversion of buprenorphine is the potential that the medication may be used by individuals experimenting with illicit substances, by individuals initiating injection administration of drugs, or by individuals who are initiating opioid use [80, 81]. In Georgia, 11.5% of IDUs reported that buprenorphine was their first drug of dependence [116], and in France, data suggest that the introduction of buprenorphine may have contributed to polydrug use among existing injectors [74]. In a recent study in India,

new initiates of injection were more likely to inject buprenorphine than heroin, which may be explained by the relatively recent introduction of buprenorphine to that country [104], in comparison to other opioids, such as heroin, that have been available for many decades. These data on initiation of injection with buprenorphine in India may be indicative of the social acceptability of injecting a prescription medication (buprenorphine), as opposed to a totally illicit drug (heroin), may indicate changes in the general social acceptability of injection drug use, and/or may reflect the simple fact that buprenorphine was not available when older IDUs first started injecting opioids. Further research is needed to understand buprenorphine's role in the initiation of injection drug use in India. In contrast, in a study of a national sample of drug users in the United States conducted by some of the authors of this review, initiation of injection was rare with buprenorphine and co-initiation of heroin use and buprenorphine was also rare, especially compared to other prescription opioids that were more commonly co-initiated (methadone pills, hydromorphone, oxycodone) [119].

In comparison to other opioids, the risks associated with buprenorphine diversion are relatively low. Data indicate that primary buprenorphine injectors do not inject more frequently than heroin injectors [87] and the euphoric effects of buprenorphine are low in comparison to full agonists like heroin, oxycontin, hydrocodone, morphine, or methadone [67, 120, 121]. In comparison to non-prescription opioids (like heroin), buprenorphine allows users to know the precise dose they are taking and minimizes the risks of other agents that may be introduced into non-prescription opioids [87].

Collectively these studies examining the risk profiles of buprenorphine users demonstrate that there is no reason to conclude that buprenorphine users experience any greater risk of HIV infection or transmission than other IDUs. It is entirely probable that buprenorphine injectors are at lower risk of HIV infection due to safer injection practices. This may be the result of less severe withdrawal (in comparison to full agonists) [41] or the long duration of buprenorphine's effects [122], which may consequently elicit less desperation, could provide the user with more time to obtain and prepare the next injection, and may result in a lower degree of willingness to engage in risky behavior. Further research is needed to assess relative risks of HIV infection for buprenorphine injectors and other IDUs, and to differentiate between the effects of buprenorphine on HIV transmission and the characteristics of buprenorphine injectors that may put them at a decreased risk of HIV infection.

Concomitant Drug Use and Overdose with Buprenorphine

Concomitant drug use with buprenorphine can present unique medical concerns for the user, particularly when buprenorphine is combined with benzodiazepines. Overdoses caused solely by buprenorphine are rare [123], with most overdoses occurring when the medication is used concomitantly with benzodiazepines or other sedatives [31, 37] (see Table 1). Despite reports of overdoses involving buprenorphine and benzodiazepines, rates of overdose have declined by 79% since the introduction of buprenorphine in France [31] and buprenorphine-related deaths in France, when recorded, are commonly among out-of-treatment (illicit) buprenorphine users [124].

It is important to note that rates of opioid overdose with buprenorphine are significantly lower than those associated with methadone [123], due in part to buprenorphine's ceiling effect, action as a partial agonist, and limited respiratory depression [20]. A study examining the relative rates of buprenorphine and methadone deaths in France found that the death rate attributable to methadone was at least three times greater than that of buprenorphine; the authors estimated that if all French buprenorphine patients had been treated with methadone instead of buprenorphine, there would have been approximately 288 deaths from 1994 to

1998, compared to the 46 deaths that occurred while those patients were in buprenorphine treatment [125].

DISCUSSION

Is There Sufficient Evidence to Conclude That Buprenorphine Diversion is a Problem?

Numerous studies have documented the presence and, in some instances, the extent of buprenorphine diversion in varying locations around the world. Although the phenomenon of buprenorphine diversion is now well established, the literature still lacks a complete explanation and understanding of the motivations for diversion, therapeutic applications of diverted buprenorphine, and the sources of illicit buprenorphine. As with other abuseable medications, in any location where buprenorphine is available, diversion will likely occur. However, discussions of diversion should be broadened beyond the risks or legal implications associated with this activity. Strong consideration should also be given to the medical, social, public health, and economic benefits that arise when opioid-dependent individuals use buprenorphine in a therapeutic manner to self-treat addiction and withdrawal symptoms or as a harm reduction approach to manage the risks associated with drug dependence. Any consideration of diversion should balance the overall benefits—both those seen in clinical patients as well as those seen in illicit users—with the potential harms.

Do the Benefits of Buprenorphine Outweigh the Risks?

As demonstrated in this review article, buprenorphine has the potential to be a drug of abuse, and is indeed the major drug of abuse in some geographical areas. Simultaneously, the clinical efficacy of buprenorphine for the treatment of opioid dependency has been established, and hundreds of thousands of patients have benefited from its clinical applications and accessibility. Furthermore, evidence presented in this review indicates that non-medically supervised buprenorphine is frequently used in a therapeutic manner to self-treat opioid addiction or withdrawal symptoms in individuals who cannot otherwise access substance abuse treatment, or who do not want to do so. Illicit use of buprenorphine by IDUs may also represent a harm reduction approach to reduce the consumption of other opioids, including the injection use of heroin. Additionally, misuse of buprenorphine—such as improper dosing, inhalation, or injection—among patients enrolled in buprenorphine treatment may be a sign of insufficient dosing or dissatisfaction with care. Such episodes of noncompliance may represent an opportunity for providers to adjust opioid substitution treatment to better meet the needs of buprenorphine patients.

The relative benefits and risks of buprenorphine should also be compared to those of other opioids. The abuse liability of buprenorphine and its potential for overdose mortality are less than that of full opioid agonists [61, 62, 94]. Additionally, buprenorphine precipitates withdrawal when used by opioid-dependent individuals who have other opioids in their systems, even if the buprenorphine is not coformulated with naloxone [94].

Finally, buprenorphine’s appeal to individuals with opioid addiction is an important reason to maintain and expand access to buprenorphine. Participants in several studies have expressed greater interest in engaging in buprenorphine and continuing buprenorphine treatment in comparison to methadone, have stated that they would only access buprenorphine and would not utilize methadone, and have stated a desire to switch from methadone treatment to buprenorphine treatment if possible [126, 127]. These studies collectively demonstrate the appeal of buprenorphine to many opioid-dependent individuals and indicate the need for accessible, community-based buprenorphine treatment.

Should There be Tighter Control/Monitoring of Buprenorphine?

Tighter controls on buprenorphine will likely increase barriers encountered by opioid-dependent individuals as they seek treatment, may force "black market" sales of buprenorphine into more reclusive and dangerous settings, and may result in the sale of tainted or counterfeit medications to individuals who are seeking illicit buprenorphine for therapeutic purposes. Thus, any increases in control or monitoring should be considered in parallel with efforts to increase access to affordable and sustainable opioid substitution therapy for dependent individuals.

Prescription monitoring programs (PMPs), which allow clinicians and pharmacists to conduct real-time database queries in order to verify a patient's medication dosing and detect prescription alteration and "doctor shopping", present one opportunity to approximate levels of buprenorphine diversion and misuse. PMPs have the potential to alert public health officials to potential epidemics of abuse and develop responses to engage illicit buprenorphine users in formal treatment programs. Integrated monitoring, using novel information sources like poison control centers, emergency departments, physicians, community pharmacists, and medical examiners, can be used to identify emerging epidemics of buprenorphine "doctor shopping," diversion, and misuse, allowing public health officials to direct resources toward targeted interventions [63, 96, 128, 129]. Although many existing and developing systems can provide useful information at a state or regional level, more localized surveillance could help to better identify areas with a high prevalence of buprenorphine misuse [98]. In some locations with significant problems regarding the misuse of prescription opioids, such as the United States, existing prescription monitoring programs could incorporate efforts to monitor buprenorphine. In nations where prescription drug diversion is not a major concern, infrastructure many not exist to monitor buprenorphine diversion using PMPs. Additionally, in developing countries and resource-limited settings, PMPs may not be a feasible way to monitor diversion. In any location with a PMP, more active surveillance should also be directed to help physicians engage in safer prescribing practices.

Monitoring of individuals who use buprenorphine, either through directly observed therapy (DOT) or electronic monitoring that records the date and time of medication utilization, could provide another alternative to ensuring compliance with buprenorphine treatment, following a similar model to some antiretroviral adherence studies for HIV-positive individuals in the U.S. In Finland, Tacke and colleagues recently reported on a pilot study examining the feasibility and acceptability of electronic monitoring, using a device that registers the time and date of tablet removal in a study sample of 12 buprenorphine patients. The technology was well accepted and participants reported increased adherence to their treatment plans and decreased diversion of buprenorphine [130]. The costs associated with electronic monitoring devices may be unreasonable in resource limited settings, in locales where patients must pay for their own treatment, or where insurance companies or government agencies are hesitant to burden the extra cost.

Another approach to decrease the street demand for illicit buprenorphine could be to increase availability of buprenorphine and buprenorphine/naloxone. Market economic principles would suggest that, with greater availability, cost could decrease and access to care and utilization of care could increase. This could potentially decrease the demand for illicit buprenorphine.

Novel and Alternative Delivery Systems for Buprenorphine

Novel and alternative delivery systems could represent an innovative way to decrease buprenorphine diversion without compromising access to affordable care. One example is

alternate day dosing with sublingual buprenorphine, which was shown to be clinically effective, feasible, and acceptable to patients over the past two decades [131–133]. In situations where health care professionals directly observe patient dosing with buprenorphine, alternate day dosing has the potential to allow patients to make fewer trips to the dosing location and requires less contact time for health care professionals. Also, in locations where diversion of buprenorphine take-home doses is an issue, alternate day dosing at a medical facility could help to curtail diversion.

Clinical trials with Probuphine®, which utilizes sustained release technology in a hard-to-extract subdermal implant, have shown steady blood levels of buprenorphine for at least six months and little evidence of withdrawal [134]. Anecdotal evidence from trial participants also indicates a preference for the subdermal product because of its lack of opioid effect and absence of withdrawal symptoms [134]. Larger trials will be required before this product can be utilized on a widespread basis.

Although many people who use buprenorphine therapeutically consume the medication sublingually, it has been noted that IDUs who inject buprenorphine to alleviate withdrawal symptoms may experience the same level of improvement as those who take it sublingually [87]. In their 2008 manuscript, Aitken *et al*. suggest that an injectable form of buprenorphine could be developed and prescribed by physicians for use in a community setting [87]. Further examination of the diversion potential, patient acceptability, clinical efficacy, and physician opinion of an injectable form of buprenorphine would be necessary before such an option could be offered to opioid-dependent IDUs.

Transdermal buprenorphine has also been studied, and could be utilized during acute detoxification. Recent studies have shown that transdermal buprenorphine is safe, well-tolerated, and clinically effective for heroin detoxification, suggesting that a 7-day application of transdermal buprenorphine may be an effective mode of opioid detoxification [135, 136].

The introduction of buprenorphine/naloxone combination product to areas that are currently experiencing buprenorphine monoproduct diversion could reduce levels of diversion, although this approach has not been validated by field experience [55]. The naloxone component of buprenorphine/naloxone, which should precipitate withdrawal if injected by opioid-dependent individuals [22–25], could result in lower levels of abuse and a lower street value than buprenorphine monoproduct. In locations that do not currently allow the use buprenorphine or buprenorphine/naloxone, initial introduction of buprenorphine/naloxone may result in lower levels of abuse than what might be expected with the sole introduction of buprenorphine monoproduct. In such areas, initial negative experiences with the misuse of buprenorphine/naloxone may result in a low desirability and demand for illicit buprenorphine and/or buprenorphine/naloxone.

Additionally, Reckitt-Benckiser, the manufacturer of brand name Suboxone® and Subutex®, recently received approval to market Suboxone® film in the United States [137]. New research examining buprenorphine diversion should consider the abuse potential of this form of buprenorphine.

AREAS FOR FURTHER RESEARCH

Research is still needed to understand the motivating factors for the diversion, abuse, and non-medically supervised use of buprenorphine, particularly in a context that is consistent with the medication's therapeutic purpose. Novel, longitudinal research is also needed to understand the long-term implications of illicit buprenorphine use, including but not limited to its effects on HIV-risk behavior and treatment seeking behavior for opioid dependence.

Future clinical investigations could also examine the feasibility and efficacy of intermittently prescribed buprenorphine for individuals who are interested in abstaining from illicit opioid use but who are unwilling or unable to enter formal treatment. More clinical research is needed to understand the efficacy, capabilities, and safety and diversion concerns of novel forms of buprenorphine, including subdermal and transdermal patches and implants and Suboxone film.

Also, more data are needed to understand the involvement of buprenorphine in overdose events (particularly when used concomitantly with other substances), to assess other adverse consequences, and to describe specifics as to why individuals inject buprenorphine, including the role of injection buprenorphine in the drug use profiles of polydrug users. Complications arising from injection buprenorphine use should be further investigated to determine whether complications are unique to buprenorphine, a result of poly-drug use, or are simply complications that can be expected of any injection drug use.

Countries that limit the number of patients per provider, such as the United States, should critically examine these limits and assess their influence on provider availability and clinical efficacy—expanding the number of patients allowed under these limits or removing them entirely may provide enhanced access to buprenorphine treatment.

Additionally, countries currently offering directly observed therapy (DOT) buprenorphine could examine the possibility of a transition to buprenorphine/naloxone, which may allow for expanded access, take-home dosing, and/or a lower level of abuse potential. Finally, future research could also examine the potential impact of over-the-counter sale of buprenorphine or buprenorphine/naloxone, especially in locations where access to prescribers is limited. More quantitative, qualitative, and ethnographic research and data are needed on an international level to understand all of these issues.

CONCLUSIONS

Opioid abuse and dependency exert an important and pressing social, economic, and biomedical toll throughout the world. Opioid substitution therapy has been proven to reduce illicit opioid use, lower rates of arrest and recidivism, decrease rates of disease transmission, and increase treatment compliance for co-occurring morbidities [15, 138–140]. Buprenorphine (Subutex® or generic) and buprenorphine/naloxone (Suboxone®) are clinically safe and effective for the treatment of opioid dependency [13, 25, 36, 94, 138, 141]. Buprenorphine's safety profile, ceiling effect at high doses, ability to be coformulated with naloxone to limit injection abuse, and lower abuse potential compared to full opioid agonists make it a suitable medication for office-based treatment of opioid dependency.

Wherever there is access to any medication with abuse potential, diversion is likely to follow, making it unsurprising that buprenorphine diversion has been documented. In the face of documented diversion, it is important to remember that buprenorphine is a clinically effective and safe medication for the treatment of opioid dependence, with considerably lower risk potential than other opioids.

Ultimately, introduction of buprenorphine to over 40 countries throughout the world has increased access to an essential medication and helped hundreds of thousands of individuals regain stability in their lives and avert negative health consequences associated with opioid abuse and injection. These benefits—whether achieved through access to a legitimate prescription or through the therapeutic use of diverted buprenorphine on the street—should be considered, such that any attempt to limit the diversion and illicit use of buprenorphine does not result in a concomitant decrease in the accessibility of this potentially life saving medicine. Extensive efforts should be made to ensure adequate accessibility to affordable

buprenorphine programs as an option for all individuals with opioid dependence and to engage individuals who are currently self-treating opioid dependence with diverted buprenorphine in formal treatment programs with proper medical and psychosocial support.

DEFINITIONS

In this document, the term “non-medically supervised use” refers to use that approximates reasonable clinical use (sublingual administration). In contrast, the terms “misuse” and “abuse” refer to the use of buprenorphine, either alone or in combination with other drugs, to attain euphoria or “get high,” and also refer to instances of buprenorphine use in a dangerous manner (for example, by intravenous administration). “Diversion” refers to the act of redirecting buprenorphine or buprenorphine/naloxone from legitimate sources to illegitimate or illegal ones. The term “buprenorphine” refers to the buprenorphine mono-product (Subutex®), whereas “buprenorphine/naloxone” refers to the coformulated product (Suboxone®). Suboxone® is coformulated in a 4:1 ratio of buprenorphine to naloxone, and is available in 2mg/0.5mg and 8mg/2mg doses. Subutex® is generally available in 0.4mg, 2mg, and 8mg doses.

Although buprenorphine diversion, abuse, misuse, and non-medically supervised use have been examined in the current literature, manuscripts on this topic rarely explicitly define these terms.

Acknowledgments

This research was supported by grant P30-AI-42853 from the National Institutes of Health, Center for AIDS Research (NIH/CFAR), P30DA013868 from the Center for Drug Abuse and AIDS Research (NIH/CDAAR), R21CE001846-01 from the Centers for Disease Control and Prevention, National Center for Injury Prevention and Control (CDC/NCIPC), and K24DA022112 from the National Institutes of Health, National Institute on Drug Abuse (NIH/NIDA). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of NIH, NIDA, CDAAR, CFAR, CDC, or NCIPC. The authors wish to thank the reviewers for their insightful comments and thoughts on this manuscript.

ABBREVIATIONS

DATA 2000	United States Drug Abuse Treatment Act of 2000
DOT	Directly observed therapy
IDU	Injection drug user
OBT	Office-based treatment
PMP	Prescription monitoring program
SAMHSA	United States Substance Abuse and Mental Health Services Administration
SEP	Syringe exchange program
U.S.	United States
UNAIDS	United Nations Joint Program on HIV/AIDS
WHO	World Health Organization

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Key Learning Objectives

Buprenorphine and buprenorphine/naloxone are clinically effective medications for analgesic use and the treatment of opioid dependence. Diversion of buprenorphine and buprenorphine is occurring throughout the world. The reasons for the diversion of these medications are not entirely understood, but include utilization for euphoric effects and self-treatment of opioid dependence. Ultimately, buprenorphine and buprenorphine/naloxone are exciting, relatively new medications for the treatment of opioid dependence, and efforts to control diversion should be considered in concert with efforts to increase access to buprenorphine treatment for individuals with opioid dependence.

Future Research Questions

Further research is needed to gain a better understanding of the motivations for and effects of buprenorphine and buprenorphine/naloxone diversion, misuse, and non-medically supervised use. The medical risks and benefits of illicit buprenorphine use remain unclear. The implications of buprenorphine's concomitant use with other drugs (licit or illicit) and the subsequent risk of overdose should be examined in further detail. Finally, new research is needed to examine the efficacy of existing diversion control measures and to understand the potential impact of new formulations of buprenorphine on diversion.

Table 1

Selected Studies Examining Buprenorphine Diversion from Various Geographic Locations

Author (Reference Number)	Year of Publication	Location	Study Type	Population	Buprenorphine (B) or Buprenorphine/ Naloxone (B/N)	Key Findings and Conclusions
Aitken [87]	2008	Australia	Cross-sectional data from a prospective longitudinal cohort	316 active injection drug users	B	32% of IDUs reported injected buprenorphine within the last 3 months and 10% reported buprenorphine as their primary drug of injection. Current enrollment in buprenorphine therapy was significantly associated with buprenorphine injection. Authors report that some buprenorphine injectors may have similar benefits in wellbeing in comparison to those who only use buprenorphine orally
Alho [79]	2007	Finland	Cross-sectional survey	176 attendees at a needle exchange program	B and B/N	73% of respondents reported buprenorphine as their most commonly used injection drug. 68% of respondents had tried buprenorphine/ naloxone *via* IV administration, but the majority (80%) reported having a bad experience. 11% reported using IV buprenorphine for “euphoria or pleasure,” while 73% reported doing so “to treat my addiction”
Auriacombe [31]	2004	France	Literature review	N/A	B	About 65,000 patients are treated with buprenorphine each year. IV buprenorphine may occur in up to 20% of those treated with the medication. Opioid overdose rates have declined 79% since buprenorphine’s introduction in 1995
Bazazi [101]	2011	USA	Cross-sectional survey	51 injecting and 49 non-injecting out-of-treatment opioid users	B/N	A majority (76%) reported ever obtaining buprenorphine/naloxone illicitly, with a majority using the illicit medication for therapeutic purposes. More IDUs than non-IDUs reported using illicit buprenorphine/ naloxone for these purposes, while more non-IDUs than IDUs reported using buprenorphine to “get high.”
Bruce [55]	2009	Malaysia	cross-sectional survey	41 buprenorphine/ nal oxone injectors who previously only injected buprenorphine	B and B/N	The authors assessed the introduction of buprenorphine/naloxone in a country where buprenorphine alone was previously available. The mean injection dose rose during the introduction, and participants reported the development of opioid withdrawal symptoms, which was associated with increased benzodiazepine injection and syringe sharing.
Hakansson [80]	2007	Sweden	Cross-sectional survey	350 attendees at a needle exchange program	B	89% of heroin users reported past-year buprenorphine use, of which 87% reported buprenorphine use for therapeutic purposes

Author (Reference Number)	Year of Publication	Location	Study Type	Population	Buprenorphine (B) or Buprenorphine/ Naloxone (B/N)	Key Findings and Conclusions
						(detoxification or treatment of withdrawal) and 11% reported misusing buprenorphine for euphoria. Overall, 43% of illicit users reported consuming buprenorphine intravenously and 29% by snorting.
Kumar [114]	2000	India	cross-sectional rapid assessment	100 IDUs	B	Buprenorphine injectors were less likely to share injection equipment, to have more drug using network members, and to face threats of arrest. 42% of participants reported buprenorphine as their primary drug. 74% of buprenorphine users also reported misuse of other drugs, including benzodiazepine. Buprenorphine users did not exhibit a sense of desperation in obtaining more buprenorphine, as they did not report “agonizing” withdrawal symptoms
Schuman-Olivier [33]	2010	USA	cross-sectional analysis with a subsequent 90-day prospective longitudinal cohort	cross-sectional: 78 patients who were beginning or continuing buprenorphine treatment. prospective longitudinal cohort: 42 of the cross-sectional participants	B/N	Among those seeking treatment, 49% of participants reported using buprenorphine in the last 90 days. Of illicit buprenorphine users, 97% reported using the medication for prevent cravings, 90% reported doing so to prevent withdrawal, and 29% reporting doing so to save money. Illicit use of buprenorphine decreased when participants had access to a legitimate prescription.
Winstock [50]	2010	Australia	cross-sectional survey	448 clients who were receiving treatment at a public opioid clinic	B	27% of participants who received buprenorphine reported ever injecting it, while 66% of methadone users reported injecting methadone. 65.2% participants receiving buprenorphine preferred to take their medication as directed. 51% of participants reported that it was easier to obtain methadone on the street, in comparison to buprenorphine. The median street cost of buprenorphine was $2.50/mg. The authors suggest that new attempts to limit diversion must consider the impact on personnel, time resources, and patient acceptability