American Society of Addiction Medicine

4601 North Park Avenue ● Upper Arcade Suite 101 ● Chevy Chase, MD 20815-4520
Treat Addiction ● Save Lives

May 8, 2015

Richard G. Frank, PhD
Assistant Secretary for Planning and Evaluation
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Assistant Secretary Frank,

Thank you again for taking the time to meet with us to discuss the Secretary's plan to address the opioid overdose epidemic. As you are well aware, every day 120 people in the U.S. die as a result of drug overdose, and many more become addicted.[i] Fortunately, like other chronic diseases, opioid addiction can be prevented and the millions of Americans now suffering from this disease can be treated. We believe the Secretary's plan lays a solid foundation for a comprehensive and well-coordinated prevention and treatment effort to address one of the most grave public health threats that our country faces.

As we discussed, we're writing to provide additional information and data to support the implementation of the Secretary's plan. This letter addresses: (1) a proposed curriculum to train physicians to engage patients and refer them to treatment when PDMP data indicate a patient is seeking opioids or other drugs due to possible addictive disease, (2) a proposed pilot program to increase the DATA 2000 patient limit for addiction specialist physicians in high-need areas, and (3) research on risk factors for buprenorphine diversion.

In addition to the information below, ASAM's forthcoming National Practice Guideline on Medications for the Treatment of Addiction Involving Opioid Use will be a valuable resource for physicians, payers and policymakers who want to ensure that patients with opioid addiction receive high-quality, evidence-based treatment. We will be very happy to share a copy of the guideline with you once it is finalized next month.

1. PDMP Patient-Engagement Curriculum

As the Secretary's plan recognizes, prescription drug monitoring programs (PDMPs) have the potential to help clinicians identify high-risk patients and positively impact prescribing behaviors. While increased use, interoperability and real-time data, as called for in the Secretary's plan, are crucial steps to making PDMPs

more effective, prescribers also need to be trained in how to engage patients whose prescription data indicate they are at risk for addiction and refer them to treatment. Too often, these patients are dismissed without meaningful patient interaction and referral to treatment, leaving them to seek drugs elsewhere, often on the street. In no other area of medicine is it acceptable for physicians or other clinicians to diagnose a patient and then dismiss that patient or fail to refer him or her to treatment.

To close this gap, **we recommend developing a national prescriber training curriculum that would equip users of PMDPs to engage at-risk patients and refer them to treatment**. The training could cover not only risk factors and additional screening techniques for substance use disorders and a basic overview of the bio-psycho-social characteristics of addiction, but importantly teach strategies for engaging patients and talking to them about their substance use and the kinds of treatment which might be indicated depending on further assessment of their condition, as well as additional resources available to help providers effectively refer patients to treatment. The training could be made available via webinar, as a point-of-care resource when patients are identified through the PDMP and in-person at gatherings of medical professionals, with initial roll-out targeted to states where the opioid overdose epidemic is most severe.

As a member of the CO*RE Collaborative[ii] which includes 10+ professional societies and which has reached over 75,000 clinicians through the ER/LA REMS training, ASAM and its CO*RE partners are well-positioned to design, develop and implement such a curriculum. We would be happy to speak further with the Department and other stakeholders about how CO*RE could help to meet this educational need.

2. DATA 2000 Pilot Program

Patients face many barriers to accessing high-quality addiction treatment, including insufficient insurance coverage, social stigma, privacy concerns, a misunderstanding of the disease and a lack of information on how to get help.[iii] Crucially, of those individuals who are able to access some sort of addiction treatment, only a small fraction of individuals receive interventions or treatment consistent with scientific knowledge about what works. One component of this gap between science and practice is the underutilization of pharmaceutical treatments.[iv]

Despite a significant body of evidence supporting its safety[v], effectiveness and cost-effectiveness,[vi] buprenorphine in particular is significantly underutilized in the treatment of opioid addiction.[vii] Physicians report that cost, lack of insurance coverage, and lack of availability at pharmacies are obstacles to treating patients with buprenorphine, but physician bias against patients with addiction contributes to the treatment gap as well.[viii]

Exacerbating this gap is the limit on the number of patients to whom a physician can prescribe buprenorphine, established by the Drug Addiction Treatment Act (DATA 2000). While many physicians may feel inadequately trained to treat or hold biases against patients with addiction and choose not to treat them, addiction physician specialists have the expert training and willingness to treat this complex patient

population. Yet, unlike their use of any other FDA-approved medication, they may only prescribe to a maximum of 100 patients (or 30 patients in their first year of prescribing). In a 2013 survey of ASAM members, a unique subset of physicians who specialize in addiction treatment, 43.8% of respondents indicated they had demand for buprenorphine treatment that exceeded the 100 patient limit.

To help meet the demand for evidence-based addiction treatment in areas hardest hit by the opioid overdose epidemic, we propose creating **a pilot program to allow addiction physician specialists to treat more than 100 patients with buprenorphine**. This program could be targeted to those geographic areas with a clear need for additional treatment capacity, as evidenced by overdose death rates, and limited to those physicians with advanced specialty training in addiction, as evidenced by sub-specialty board certification and ongoing maintenance of certification, to ensure that patients are receiving care by appropriately educated providers. With the upcoming publication of ASAM's "National Guidelines for the Use of Medications in the Treatment of Addiction Involving Opioid Use," these guidelines may be used to ensure evidence-based, high quality care with diversion control protocols to be in place in the pilot programs. If possible, the utilization of Advance Practice Clinicians under the supervision of these highly educated physician specialists could also assist in determining the quality of care provided by this expanded prescribing group.

Such a pilot program could offer insights into the feasibility and desirability of lifting the DATA 2000 patient limit more broadly, either to additional geographic regions or additional physician specialties. Most importantly, it is an immediate, actionable step to expand access to evidence-based treatment for those patients where the need is greatest while keeping safeguards in place to prevent the proliferation of buprenorphine "pill mills."

ASAM would be very happy to work with the Secretary to develop the details of this pilot program so that it may be implemented during her tenure.

3. Buprenorphine Diversion

Buprenorphine diversion is a legitimate concern as we consider expanding access to it. With increased availability comes increased risk of diversion and misuse. Indeed, National Forensic Laboratory Information System (NFLIS) seizures (representing diverted buprenorphine) increased from 446 in 2005 to 6722 in 2009 as use in office-based opioid treatment increased.[ix]

However, it's important to know what drives diversion if we are to prevent it effectively. In a recent prospective study of diverted buprenorphine use, Lofwall and Havens found that **the strongest predictor of diverted buprenorphine use was attempting but failing to access buprenorphine treatment.**[x] This suggests that increasing, not limiting, buprenorphine treatment access may be an effective response to buprenorphine diversion among persons not in treatment. Moreover, and more generally, high-quality office-based opioid dependence treatment has been shown to reduce illicit opioid use and increase drug abstinence.[xi] Thus, ensuring affordable

access to such care has the potential to reduce the diversion and misuse not only of buprenorphine, but of all opioid analgesics.

We hope this information proves helpful, and we look forward to continuing to work with you and your HHS colleagues as the Secretary's plan is implemented. Please don't hesitate to reach out if we can provide further information or be of assistance in any way. We're grateful for your leadership on this important issue.

Sincerely,

Kelly J. Clark, MD, MBA, DFAPA, FASAM
President-Elect, American Society of Addiction Medicine

Attachments:

1. Lofwall, M.R., & Havens, J.R. (2012). Inability to access buprenorphine treatment as a risk factor for using diverted buprenorphine. *Drug Alcohol Depend*, 126(3):379-83.
2. Lofwall, M.R., & Walsh, S.L. (2014). A Review of Buprenorphine Diversion and Misuse: The Current Evidence Base and Experiences From Around the World. *J Addict Med,* 8(5):315-326.

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[ii] For more information about CO*RE: http://www.core-rems.org/
[iii] The National Center on Addiction and Substance Abuse at Columbia University. Addiction Medicine: Closing the Gap between Science and Practice. June 2012.
[iv] *Ibid*.
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[x] *Ibid.*
[xi] *Ibid.*

Inability to access buprenorphine treatment as a risk factor for using diverted buprenorphine

Michelle R. Lofwall[1,2] and **Jennifer R. Havens**[2,3]

[1]Department of Psychiatry, University of Kentucky College of Medicine, Lexington, Kentucky

[2]Center on Drug and Alcohol Research, Department of Behavioral Science, University of Kentucky College of Medicine, Lexington, Kentucky

[3]Department of Epidemiology, University of Kentucky College of Public Health, Lexington, Kentucky

Abstract

Background—As buprenorphine prescribing has increased in the United States so have reports of its diversion. The study purpose was to examine frequency and source of and risk factors for diverted buprenorphine use over a 6-month period in an Appalachian community sample of prescription opioid abusers.

Methods—There were 503 participants at baseline; 471 completed the 6-month follow-up assessment. Psychiatric disorders and demographic, drug use, and social network characteristics were ascertained at baseline and follow-up. Multivariable logistic regression was used to determine the predictors of diverted buprenorphine use over the 6-month period.

Results—Lifetime buprenorphine use “to get high” was 70.1%. Nearly half (46.5%) used diverted buprenorphine over the 6-month follow-up period; among these persons, 9.6% and 50.6% were daily and sporadic (1–2 uses over the 6-months) users, respectively. The most common sources were dealers (58.7%) and friends (31.6%). Predictors of increased risk of use of diverted buprenorphine during the 6-month follow-up included inability to access buprenorphine treatment (AOR: 7.31, 95% CI: 2.07, 25.8), meeting criteria for generalized anxiety disorder, and past 30 day use of OxyContin, methamphetamine and/or alcohol.

Conclusions—These results suggest that improving, rather than limiting, access to good quality affordable buprenorphine treatment may be an effective public health strategy to mitigate buprenorphine abuse. Future work should evaluate why more persons did not attempt to access treatment, determine how motivations change over time, and how different motivations affect diversion of the different buprenorphine formulations.

Corresponding Author: Michelle R. Lofwall, Center on Drug and Alcohol Research, 515 Oldham Court, Lexington, KY 40502, michelle.lofwall@uky.edu, Office: (859) 323-6774, Fax: (859) 257-5232.

Contributors. Dr. Havens designed the study, wrote the protocol, and conducted the statistical analyses. Drs. Havens and Lofwall managed the literature searches, summaries of previous related work, and wrote the manuscript. Both authors contributed to and have approved the final manuscript.

Conflicts of Interest. Dr. Lofwall has received honoraria for giving continuing medical education presentations from Reckitt Benckiser Pharmaceutical (RBP) and has received an investigator-initiated research project grant from RBP in the last three years.

Keywords

diversion; prescription opioids; buprenorphine; abuse; opioid dependence treatment

1. Introduction

Office-based opioid dependence treatment (OBOT) with buprenorphine (non-generic and generic buprenorphine tablets, and non-generic buprenophine tablets and film) in the United States (US) has grown considerably since its Food and Drug Administration approval in 2002. In 2010 there were approximately 500,000 unique recipients of buprenorphine (Dart, 2011). However, with increased buprenorphine availability, there have been increased reports of buprenorphine misuse and diversion. Specifically, U.S. emergency department (ED) visits related to buprenorphine misuse/abuse according to the Drug Abuse Warning Network (DAWN) increased from 5025 visits in 2006 to 17,546 visits in 2009, National Forensic Laboratory Information System (NFLIS) seizures (representing diverted buprenorphine) increased from 446 in 2005 to 6722 in 2009, and Poison Control Center exposures increased from 765 in 2006 to 3212 in 2009. These increases were primarily, but not entirely, accounted for by the increased amounts of non-generic buprenophine tablets sold over these years (Johanson et al., 2012). Specifically, there were an excess of 20 DAWN ED visits, 46 NFLIS seizures, and 23 Poison Control Center exposures per year for each additional million tablets sold per year.

Determining risk factors for use of diverted buprenorphine is a critical step in order to develop public health strategies to mitigate this adverse event. Studies in France show that prior drug use by intravenous and intranasal routes predict buprenorphine misuse via intravenous and intranasal routes, respectively (Roux et al., 2008a; Roux et al., 2008b; Vidal-Trecan et al., 2003). However, there are no prospective data regarding predictors of diverted buprenorphine use within the US. Thus, the purpose of this study was to prospectively evaluate the risk factors, frequency and source of buprenorphine used among a community sample of prescription opioid abusers. Both individual and social network-level characteristics were examined. Social networks influence drug use initiation and continuation (Valente et al., 2004), but their role in buprenorphine diversion has not yet been evaluated.

2. Methods

2.1 Study design and population

This prospective analysis is nested within an ongoing longitudinal cohort study of social networks and HIV risk among rural Appalachian drug users. Inclusion criteria included: 1) age 18 years or older; 2) residing in an Appalachian Kentucky county; and 3) recent (i.e., last 30-day) use of prescription opioids, heroin, cocaine and/or methamphetamine. Participants were compensated $50 per study visit. The University of Kentucky Institutional Review Board approved the study.

2.2 Sampling

The cohort was recruited using Respondent Driven Sampling (RDS) that is effective in recruiting hard-to-reach populations, including rural drug users (Heckathorn, 1997; 2002; Wang et al., 2007). Initial recruits (i.e., seeds) were identified through community outreach, word-of-mouth, and flyers. Each seed was given three coupons with which to recruit their peers. Seeds received $10 for each redeemed coupon. Recruited peers then were asked to recruit their peers and so on, until the desired sample size was reached (n=503).

2.3 Variables and Measures

Trained non-clinician interviewers conducted baseline and 6-month follow-up interviews. Baseline questionnaires included the Addiction Severity Index (McLellan et al., 1992) and the Mini-International Neuropsychiatric Interview (MINI), version 5.0 (Sheehan et al., 1998). Demographic variables, collected by the ASI, included gender, age, years of education, legal income, current marital (married/unmarried) and employment status (see Table 1 for categories), and race (white/non-white). ASI drug use variables included number of previous detoxification and drug treatment episodes, recent number of days with drug problems, recent number of days using several drugs (see Table 1 for specific drugs queried) received by illegal (i.e., not prescribed) and legal (i.e., prescribed) means. The MINI determined whether Diagnostic and Statistical Manual of Mental Disorders criteria were met for current major depressive disorder (MDD), generalized anxiety disorder (GAD) and antisocial personality disorder (ASPD). Participants also were asked “Have you ever attempted, but were unable to get into buprenorphine treatment?” A name-generating questionnaire determined the total number of persons in each participant’s social network with whom the participant used drugs (drug network), had sex (sex network) and counted on for social support (support network) in the past 6-months. These characteristics listed above served as independent variables for subsequent analyses. In addition, participants were queried about their primary source for buprenorphine.

At the 6-month follow-up visit subjects were asked if they had ever used buprenorphine (non-generic buprenophine, generic buprenorphine tablets, and buprenorphine and naloxone to get high. If the answer was “yes,” frequency of non-prescribed (i.e., diverted) use was determined over the last 6 months and 30 days. The dependent variable analyzed was past 6-month use of diverted buprenorphine (yes/no).

2.4 Analytic Plan

Descriptive statistics are provided on the prevalence, frequency and source of diverted buprenorphine used. Chi-square tests and Wilcoxon rank-sum tests for categorical and continuous variables, respectively, were completed comparing characteristics of those who reported any past 6-month diverted buprenorphine use to those who reported none. As participants were nested within social networks, a variance component model evaluated whether diverted buprenorphine use differed across network components; results showed it did not. Thus, multivariable logistic regression was employed to model the risk factors (see Table 1 for list of independent variables) for any past 6-month diverted buprenorphine use. Variables significant at the $p<0.10$ level in unadjusted models were entered into the multivariable logistic model one at a time from most to least significant. Only variables significant (i.e., $p<0.05$) were retained in the final model. STATA, version 12.0 was utilized for all analyses.

3. Results

There were 503 participants at baseline; all reported past 30-day non-medical prescription opioid use “to get high.” Ninety-three percent (n=471) completed the 6-month follow-up interview and were included in the results reported here. The majority reported using buprenorphine “to get high” at least once in their lifetime (70.1%; n=330). Nearly half (46.5%; n=219) had used diverted buprenorphine between the baseline and 6-month follow-up visit; most (50.7%; n=111) were sporadic users, reporting 1–2 uses over this time period. Daily use was uncommon (9.6%; n=21). The median number of days of diverted buprenorphine use in the last 30 days was 1 (interquartile range: 0, 3). The most common primary sources of buprenorphine were: dealer (58.7%) and friends (31.6%), followed by

family (7.3%) and spouse/partner (1.4%). Physicians were rarely (0.9%) a primary source as expected.

Table 1 shows the baseline characteristics among those who did (n=219) and did not (n=252) report any past 6-month use of diverted buprenorphine. Median and interquartile range (IQR) of monthly legal income did not differ (p=0.781) between those who had used diverted buprenorphine [$500 (IQR: 150, 900)] and those who had not [$573 (200, 900)]. The only sociodemographic difference between these two groups was being on disability, which decreased the odds of having used diverted buprenorphine compared to the unemployed. Recent use of OxyContin, hydrocodone, methamphetamine and alcohol at baseline increased, while recent use of benzodiazepines decreased, the odds of having used buprenorphine. Injection drug use (IDU) and meeting criteria for GAD at baseline, and attempting but failing to access buprenorphine treatment (p=0.001) also were significant risk factors. Lastly, for each additional member of one's drug network, the odds of using diverted buprenorphine increased 5%.

In the adjusted model (Table 2), six variables emerged as significant predictors of diverted buprenorphine use over the 6-month period. The strongest predictor was attempting but failing to access buprenorphine treatment (Adjusted Odds Ratio [AOR]: 7.31, 95% Confidence Interval [CI]: 2.07, 25.8). Meeting criteria for GAD and recent use of OxyContin, methamphetamine, and alcohol at baseline also were independent risk factors. Recent benzodiazepine use was associated with decreased risk (AOR: 0.53, 95% CI: 0.31, 0.89). Drug network characteristics and being on disability were not significant variables in the adjusted model.

4. Discussion

This study prospectively evaluated risk factors for diverted buprenorphine use in a community-based sample of prescription opioid abusers in the US. Attempting but failing to access buprenorphine treatment was the strongest predictor of diverted buprenorphine use over the 6-month period, increasing the risk 7-fold. Notably, daily use of diverted buprenorphine was uncommon (i.e., n=21 of 471 or 4.5% of the sample).

The finding that the most robust risk factor for buprenorphine use was failing to access legitimate buprenorphine treatment has several important implications. First, it suggests that increasing, not limiting, buprenorphine treatment access may be an effective response to buprenorphine diversion among persons not in treatment. However, it is noteworthy that relatively few participants (n=19) overall attempted to access buprenorphine treatment suggesting a need to understand better why more persons were not attempting to access OBOT. One potential reason is that the cost of OBOT is too high for this sample; monthly legal incomes were approximately $500 yet the cost of OBOT treatment in Kentucky (KY) is on average $940/month [e.g., 16 mg/day of buprenorphine and naloxone film costs ~$540 at KY Walmart stores and the largest provider of OBOT in KY charges ~$400/month].

Other inventions also are likely needed to mitigate diversion. Dealers and friends were the most common source of diverted buprenorphine in this sample. Friends and family were the most common sources of non-medical use of prescription opioids in the National Survey on Drug Use and Health, but the majority of the friends and family had received them from doctors' prescriptions (SAMHSA, 2009). Thus, it is possible that doctors are an indirect source of diverted buprenorphine and could benefit from continuing educational activities targeted at improving current OBOT practices. For instance, there are data showing that doctors providing OBOT in Appalachia as well as other US regions have limited understanding of the legislation allowing for OBOT, the clinically relevant pharmacology of

buprenorphine, and many were not engaging in currently recommended OBOT practice behaviors (i.e., only 50% of doctors reported routinely inducting patients while in withdrawal; Lofwall et al. 2011). While OBOT physicians are regulated by the Drug Enforcement Administration (DEA), DEA regulation is not aimed at teaching or evaluating for quality OBOT practices. Importantly, quality care OBOT practices have been shown to reduce illicit opioid use and increase drug abstinence (Alford et al., 2011; Fiellin et al., 2008; Parran et al., 2010; Soeffing et al., 2009). Thus, OBOT has the potential to not only reduce buprenorphine diversion and misuse, but also diversion and misuse of the prescription opioid analgesics that have been associated with increasing unintentional overdose deaths (Hall et al., 2008; Paulozzi et al., 2006; Paulozzi and Ryan, 2006).

Recent oxycodone use also was a risk factor for diverted buprenorphine use. Oxycodone abuse is highly prevalent in Appalachia and associated with a more severe profile of drug problems compared to abuse of other prescription opioids (Havens et al., 2007a; Young and Havens, 2012). Thus, it may be that oxycodone use is an indicator of someone with a more severe drug use disorder that is trying to use buprenorphine to relieve withdrawal symptoms and/or treat their addiction as others have reported (Alho et al., 2007; Mitchell et al., 2009; Monte et al., 2009).

Methamphetamine and alcohol use also were predictors of buprenorphine use. This fits a general pattern of poly-drug use in this cohort that is consistent with other studies among rural Appalachian drug users (Shannon et al., 2011; Havens et al., 2007b). Another interesting finding was that those with GAD were more likely to have used diverted buprenorphine. It has been speculated, although not widely accepted or proven, that buprenorphine may be effective in treating anxiety (McCann, 2008), suggesting a self-medication hypothesis to explain the results here. However, this diagnosis was made by the MINI and was not confirmed by a clinical interviewer, which is a study limitation.

Lastly, recent benzodiazepine use is clearly *not* a risk factor for use of diverted buprenorphine in this sample. While it was associated with a lower adjusted odds ratio, it would be incorrect to say that benzodiazepine use is protective because benzodiazepine use was very high (>80%) among those who did and did not use diverted buprenorphine, far greater than other buprenorphine-treated populations (e.g., 46% for Lavie et al., 2009; 32% among those in the Bramness and Kornor, 2007; and 67% for Nielsen et al., 2007). This high prevalence of benzodiazepine use is concerning because the majority of deaths with buprenorphine have occurred when combined with other central nervous system depressants like the benzodiazepines, particularly by the intravenous route (Kintz, 2001).

While lifetime buprenorphine use “to get high” was specifically queried, the motivations for use of past 6-month and recent use of diverted buprenorphine were not systematically queried. Thus, it is possible that persons were using buprenorphine for a variety of reasons such as treating their own addiction and/or opioid withdrawal as others have reported (Alho et al., 2007; Mitchell et al., 2009; Monte et al., 2009). In fact, several subjects said they were using the medication to treat their addiction and withdrawal. Future research should more clearly evaluate motivations at each use along with route of use and the formulation of buprenorphine used (e.g., film, tablet, generic or combination products). Differences in motivations and routes of use of diverted medication may vary depending on the formulation as well as the subject population (e.g., opioid dependent or not). For example, if buprenorphine/naloxone is misused by a parenteral route in an opioid dependent individual, it produces more severe precipitated opioid withdrawal compared to buprenorphine alone (Stoller et al., 2001). However, among recently detoxified and non-dependent opioid abusers, there is no statistically significant difference in self-administration of buprenorphine/naloxone compared to buprenorphine alone (Comer and Cone 2002), and

naloxone does not significantly diminish buprenorphine's opioid agonist effects when administered intranasally or sublingually (Middleton et al. 2011; Strain et al., 2000).

4.2. Conclusions

The inability of nonmedical prescription opioid users to access buprenorphine treatment was the strongest predictor of diverted buprenorphine use. However, relatively few participants attempted to access treatment overall. Therefore, understanding why there were not more attempts to access OBOT and ensuring adequate access to quality, affordable OBOT are logical next steps in attempting to reduce diverted buprenorphine use; such actions also should decrease use of other diverted prescription opioids that have been associated with the US epidemic of unintentional overdose deaths.

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Table 1

Characteristics of Prescription Opioid Abusers (n=471) who Did and Did Not Use Diverted Buprenorphine over the 6-month Follow-Up Period

Baseline Variables	**Bup Use n=219**		**No Bup Use N=252**			**Odds**	
	n	**%**	**n**	**%**	**p-value**	**Ratio**	**95% CI**
Demographics							
Female	103	47.0	104	41.3	0.209	1.26	0.87, 1.82
White	208	95.0	235	93.2	0.430	1.37	0.62, 2.99
Age in years, med (IQR)*	30 (26, 36)		32 (27, 38)		0.064	0.98	0.96, 1.00
Years of education, med (IQR)	12 (10, 12)		12 (10, 12)		0.426	1.00	0.99, 1.01
Married	54	24.7	66	26.2	0.703	0.92	0.61, 1.39
Employment:							
Unemployed	50	22.8	60	23.8	-	1.00	-
Full-Time	74	33.8	89	35.3	0.189	0.73	0.45, 1.16
Part-Time	66	30.1	58	23.0	0.236	0.73	0.44, 1.22
Disability	22	10.0	38	15.1	0.036	0.51	0.27, 0.95
Student/retired/military	7	3.2	7	2.8	0.819	0.88	0.29, 2.65
Past 30-day drug use, # days							
Legal (prescribed) methadone use	3	1.4	10	4.0	0.086	0.37	0.09, 1.24
Illegal (not prescribed) use of:							
Methadone	139	63.5	145	57.5	0.189	1.28	0.88, 1.86
OxyContin	167	76.3	162	64.3	0.005	1.78	1.19, 2.67
Other oxycodone	165	75.3	178	70.6	0.252	1.27	0.84, 1.91
Hydrocodone	188	86.2	197	78.2	0.024	1.79	1.07, 2.85
Benzodiazepines	178	81.3	222	88.1	0.039	0.57	0.35, 0.97
Alcohol	131	59.8	123	48.8	0.017	1.56	1.08, 2.25
Heroin	8	3.65	12	4.76	0.552	0.76	0.30, 1.89
Cocaine	58	26.5	49	19.4	0.069	1.49	0.97, 2.30
Crack cocaine	25	11.4	29	11.5	0.975	0.99	0.56, 1.74
Methamphetamine	12	5.6	3	1.2	0.008	4.81	1.33, 17.3
Marijuana	142	64.2	146	57.9	0.125	1.34	0.92, 1.95

Baseline Variables	Bup Use n=219		No Bup Use N=252			Odds	
	n	%	n	%	p-value	Ratio	95% CI
≥1 day of IDU in past 6 months	137	62.6	132	52.4	0.026	1.52	1.05, 2.19
Treatment							
Tried and failed to enter buprenorphine treatment (tx)	16	7.3	3	1.2	0.001	6.54	1.87, 22.7
# Days drug problems, med (IQR)	10 (0, 30)		10 (0, 30)		0.467	1.00	0.99, 1.02
# Previous tx episodes, med (IQR)	1 (0, 2)		1 (0, 2)		0.834	1.01	0.95, 1.09
# Previous of detoxs, med (IQR)	0 (0, 1)		0 (0, 1)		0.543	1.05	0.97, 1.13
DSM-IV Disorders							
Major Depressive Disorder	55	25.1	68	27.0	0.645	0.91	0.60, 1.37
Generalized Anxiety Disorder	79	36.1	61	24.2	0.005	1.77	1.18, 2.63
Antisocial Personality Disorder	76	34.7	72	28.6	0.153	1.33	0.89, 1.96
Social Network							
# Persons in Drug Network	5 (3, 10)		4 (2, 8)		0.031	1.05	1.01, 1.09
# Persons in Sex Network	2 (1, 5)		2 (1, 5)		0.273	1.01	0.97, 1.06
# Persons in Support Network	2 (1, 3)		2 (1, 3)		0.242	1.10	0.95, 1.27

*Med= median and IQR=interquartile range.

Table 2

Factors Predictive of Diverted Buprenorphine Use

	Adjusted Odds Ratio	95% Confidence Interval
Tried and failed to access buprenorphine treatment	7.31	2.07, 25.8
Past 30 Day Use of Non-Prescribed:		
OxyContin®	1.80	1.18, 2.75
Benzodiazepines	0.53	0.31, 0.89
Methamphetamine	4.77	1.30, 17.5
Alcohol	1.60	1.09, 2.36
Generalized Anxiety Disorder	1.69	1.11, 2.56

A Review of Buprenorphine Diversion and Misuse: The Current Evidence Base and Experiences From Around the World

Michelle R. Lofwall, MD and Sharon L. Walsh, PhD

Outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy has rapidly expanded in the United States and abroad, and, with this increase in medication availability, there have been increasing concerns about its diversion, misuse, and related harms. This narrative review defines the behaviors of diversion and misuse, examines how the pharmacology of buprenorphine alone and in combination with naloxone influence its abuse liability, and describes the epidemiological data on buprenorphine diversion and intravenous misuse, risk factors for its intravenous misuse, and the unintended consequences of misuse and diversion. Physician practices to prevent, screen for, and therapeutically respond to these behaviors, which are a form of medication nonadherence, are discussed, and gaps in knowledge are identified. Outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy experiences from other countries that have varied health care systems, public policies, and access to addiction treatment are shared to make clear that diversion and misuse occur across the world in various contexts, for many different reasons, and are not limited to buprenorphine. Comparisons are made with other opioids with known abuse liability and medications with no known abuse. The objective was to facilitate understanding of diversion and misuse so that all factors influencing their expression (patient and provider characteristics and public policy) can be appreciated within a framework that also recognizes the benefits of addiction treatment. With this comprehensive perspective, further careful work can help determine how to minimize these behaviors without eroding the current benefits realized through improved addiction treatment access and expansion.

Key Words: behavioral pharmacology, buprenorphine, diversion, epidemiology, misuse, treatment

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Outpatient opioid addiction treatment with sublingual buprenorphine formulations (OBOT) has expanded rapidly over the last two decades in many areas of the world. Notably, before its use in addiction treatment, sublingual (eg, Temgesic) and injectable buprenorphine (eg, Buprenex) formulations were approved for pain treatment, and multiple countries reported problems with their misuse and diversion (Morrison, 1989; Singh et al., 1992). Outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy became available in the United States later, after the passage of the Drug Abuse Treatment Act of 2000; this law allowed schedule III-V opioids approved by the Food and Drug Administration (FDA) for the treatment of opioid dependence to be prescribed by medical practitioners outside of the confines of federally licensed methadone treatment centers for the first time since the passage of the Harrison Narcotic Act in 1914. Subsequently, the FDA approved both buprenorphine (BUP) and buprenorphine/naloxone combination (BUP/NX) sublingual tablet formulations. However, many European countries, Australia, and some Asian countries had introduced BUP earlier (throughout the 1990s) and BUP/NX followed in some countries (eg, in 2006 BUP/NX was approved for use in the European Union). Generic tablet formulations have also entered various markets, and a BUP/NX film product is now available in the United States and Australia.

With the growth of OBOT and resulting increased availability of buprenorphine, concerns related to buprenorphine misuse and diversion have arisen (Center for Substance Abuse Research, 2011; Johanson et al., 2012), the extent of which

From the Center on Drug and Alcohol Research (MRL, SLW), the College of Medicine Departments of Behavioral Science (MRL, SLW), Psychiatry (MRL, SLW), and Pharmacology (SLW), and the College of Pharmacy Department of Pharmaceutical Sciences (SLW), University of Kentucky, Lexington.

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Send correspondence and reprint requests to Michelle R. Lofwall, MD, Departments of Behavioral Science and Psychiatry, Center on Drug and Alcohol Research, University of Kentucky College of Medicine, 515 Oldham Ct, Lexington, KY 40502. E-mail: michelle.lofwall@uky.edu.

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has varied widely across countries. This article will review available published evidence regarding what is known about buprenorphine product misuse, diversion, and the unintended consequences of these behaviors for patients, providers, and societies. These behaviors are influenced by an array of variables, including the pharmacological properties of the different medication formulations, patient and health care provider attitudes and behaviors, treatment structures, social and cultural expectations, and public policy. It will describe mitigation strategies that can deter misuse and diversion. Understanding the broader international experience, where both access to treatment and the structure of OBOT services differ considerably, along with the current situation in the United States may inform strategies for responding to diversion and misuse in the United States.

DEFINITIONS

For the purpose of this review and associated case conference, *BUP* specifically refers to the monotherapy sublingual tablet, *BUP/NX* to the combination tablet or film (buprenorphine with naloxone), and *buprenorphine* refers to both BUP and BUP/NX. *Diversion* is defined as the unauthorized rerouting or misappropriation of prescription medication to someone other than for whom it was intended. Diversion can occur either voluntarily or involuntarily and either with or without the exchange of money or other services (Larance et al., 2011b). *Misuse* includes taking medication in a manner, by route or by dose, other than prescribed. For instance, injecting, snorting, or smoking medication intended for oral use or double or tripling doses are both examples of misuse. Notably, these definitions do not discuss underlying motives, relatedness to addiction, treatment structure or access, or appropriate clinical responses.

BUPRENORPHINE FORMULATIONS AND THEIR PHARMACOLOGY

The primary pharmacological activity of buprenorphine in the treatment of opioid dependence arises from its partial agonist activity at the *mu* opioid receptor; however, it is also an antagonist at the kappa opioid receptor and a partial agonist at the nociceptin or nociceptin receptor (Cowan and Lewis, 1995; Bloms-Funke et al., 2000). As a *mu* opioid partial agonist, buprenorphine does not exert the same degree of intrinsic activity as a full *mu* opioid agonist, such as methadone, heroin, or oxycodone. This limit on effects at the upper end of the dose-response curve is the mechanism underlying the superior safety profile of buprenorphine compared with full *mu* opioid agonists with respect to respiratory depression and fatal overdose. This partial agonist profile has led some to suggest that buprenorphine would have reduced abuse liability compared with full *mu* agonists, but it must be recognized that buprenorphine can produce acute effects equivalent to a 60-mg dose of methadone (Walsh et al., 1994) and, thus, in individuals without physical dependence, buprenorphine is appealing for misuse and diversion. However, buprenorphine can also lead to precipitated withdrawal in opioid-dependent individuals because its high affinity/high *mu* opioid receptor occupancy, coupled with its partial agonist effects, allows it to displace other opioids occupying the receptor, while exerting insufficient activity to replace the displaced opioid's full agonist action (eg, Walsh et al., 1995). This may occur under some dosing conditions but not others (eg, Strain et al., 1992; Rosado et al., 2007) and seems to be dependent upon the maintenance opioid, the degree of physical dependence (ie, maintenance dose), the time since last dose, and the dose of buprenorphine. Precipitated withdrawal from buprenorphine can also be largely avoided by dosing only after a patient is experiencing some withdrawal (ie, when some portions of receptors are already unoccupied and agonist effects are not present).

BUP/NX was developed as an abuse-deterrent formulation. Inclusion of naloxone (which typically has very low or no sublingual bioavailability and, thus, is essentially inert when taken by the proper route) would lead to precipitated withdrawal in an opioid-dependent individual when the medication is misused by injection (and naloxone is bioavailable) (Mendelson et al., 1999; Stoller et al., 2001). Moreover, recent data have reported that intranasal administration of the BUP/NX tablets after crushing also delivers clinically relevant concentrations of naloxone (Middleton et al., 2011) that could, under some conditions, lead to precipitated withdrawal. However, more generally, the effects of naloxone are short-lived because of its short half-life (~60 minutes), and the naloxone/buprenorphine dose ratio of 1:4 is not high enough to fully block the agonist effects of buprenorphine. Numerous case reports and studies have demonstrated that there are strategies (eg, administering very small divided doses of BUP/NX) that can be used to circumvent the precipitation of withdrawal after injection of BUP/NX by opioid-dependent individuals (eg, Rosado et al., 2007; Larance et al., 2011a). Thus, the abuse-deterrent feature of naloxone in the combination product is relevant (and a deterrent) under only a subset of conditions. Although the combination formulation is the recommended formulation for providers to prescribe, research volunteers in laboratory and epidemiological studies have generally reported that when both BUP and BUP/NX are available, they prefer BUP over BUP/NX, and when full *mu* opioid agonists are available, the full agonists are preferred over both buprenorphine formulations (Strain et al., 2000; Alho et al., 2007; Degenhardt et al., 2009; Comer et al., 2010; Vicknasingam et al., 2010).

EPIDEMIOLOGY OF BUPRENORPHINE DIVERSION AND MISUSE

Buprenorphine Diversion

Numerous factors contribute to whether a particular drug is diverted for illicit use by individuals without a legitimate prescription, including, for example, drug availability, price, pharmacological properties, psychosocial and environmental factors (eg, established distribution systems and social networks), and, in the case of opioids, the degree to which dosing is supervised and the extent to which treatment demand is met (eg, see review by Bell, 2010). However, it is important to recognize that drug diversion (including sharing or selling a prescribed drug) may be a relatively common behavior, one that is not limited to those with drug dependence disorders. For example, data from the US National Household Survey on Drug Use and Health reported that nearly 17 million

persons used a prescription psychotherapeutic drug that had not been prescribed to them in the past year (Substance Abuse and Mental Health Services Administration, 2013). In a smaller national survey, 23% of those queried admitted that they shared their prescription drugs with others, whereas 27% of the sample reported that they had borrowed prescription medication from another person (Goldsworthy et al., 2008). The most commonly shared drug classes were allergy medications (25%), pain relievers (22%), and antibiotics (21%). Similar to these community-dwelling sample surveys (ie, having a substance use disorder was not required for inclusion), surveys of patients enrolled in outpatient opioid agonist programs (methadone or buprenorphine) across distinct geographical regions with widely varying treatment structures report that 18% to 28% have sold, given away their medication, removed it while under supervision, or shared other prescribed medication (Germany, 23% [Stover, 2011]; Australia, 28% [Larance et al., 2011a]; and United States, 18% [Caviness et al., 2013]). Thus, sharing and receiving prescribed medications (ie, diversion) are not unique to those with drug dependence disorders, and various medications, not only those with abuse liability, are diverted.

Regarding availability, the rapid growth and penetration of buprenorphine in the addiction medicine marketplace has increased its availability considerably over a relatively short period of time. In the United States, for example, the Automation of Reports and Consolidated Orders System, which monitors the flow of specific controlled substances from manufacture to distribution at the retail level, reports that more than 190 million dosage units of buprenorphine were distributed to pharmacies in 2010, which is more than 4-fold higher than the almost 40 million dosage units distributed just 4 years prior in 2006 (Department of Health and Human Services, 2012). Notably, only 1.1 million dosage units were distributed to licensed opioid treatment programs during 2010. Almost 800,000 individuals received prescriptions for buprenorphine from physicians with a waiver (also known as an X-license because of the marking on the Drug Enforcement Agency prescriber's license) to provide OBOT under Drug Abuse Treatment Act of 2000 in 2010, representing a nearly 5-fold increase from the 150,000 individuals estimated in 2006 (Department of Health and Human Services, 2012). Thus, the opportunity to misuse and divert buprenorphine has grown rapidly during this great expansion of OBOT.

There are limited data available that address the specific source of diverted buprenorphine. Larance et al. (2011a) reported on a cohort of out-of-treatment intravenous drug users (IVDU) in Australia who had received diverted buprenorphine. The majority reported receiving it from friends (81% BUP and 63% BUP/NX), whereas acquaintances (19% BUP and 25% BUP/NX) and dealers (19%) were reported less frequently. In this cohort, half of those receiving diverted BUP believed that it was someone's take-home dose, and the majority (71%) had paid for the drug. Interestingly, for BUP/NX, 70% believed that the dose they received was a take-home dose but fewer than half paid for it, and 48% stated that they had received the drug for free. In addition, although 12% and 9% of all BPN and BUP/NX doses dispensed, respectively, were reported as being secretly removed from the mouth during supervised dosing for later use, only a small percentage of these (9% and 13%) were removed for the purpose of selling the drug (Larance et al., 2011a).

Intravenous Misuse by Patients and Out-of-Treatment Opioid Users

Intravenous (IV) misuse will be reviewed primarily because of the significant risks associated with IVDU, including spread of infectious diseases (eg, hepatitis C and HIV), other medical complications (eg, abscess and endocarditis), and overdose. Intravenous injection of BUP and BUP/NX has been reported around the world by individuals both in and out of treatment. In a survey of individuals presenting for prescription opioid abuse treatment in the United States between 2005 and 2007 (n = 1000), 6% of participants reported injecting buprenorphine "to get high," whereas 37% of participants reported injection of other prescription opioids (eg, oxycodone) for this reason (Cicero et al., 2007). Although that study did not distinguish between BUP and BUP/NX, another surveillance system, RADARS (Researched Abuse Diversion Addiction Related Surveillance), reported past-month prevalence in the United States of IV BUP and BUP/NX misuse of 45.5% and 16.3%, respectively, by individuals presenting for opioid abuse treatment (Dart, 2011). Lower prevalence of injection of BUP/NX than of BUP has also been reported in other countries. In Australia, liquid methadone, BUP, and BUP/NX are all available treatments, and all require a period of initial supervised dosing. Among patients receiving any of these medications as part of OBOT, weekly medication injection was significantly lower for BUP/NX (7%) than for BUP (13%), but similar to liquid methadone (8%) (Degenhardt et al., 2009).

More recent data from France, where generic formulations have been available since 2006, reported significant differences in prevalence of injection of generic (5% of n = 537) versus brand name BUP (10% of n = 1159) among surveyed patients who were receiving OBOT through specialty addiction treatment clinics (ie, not by general practitioners) (Nordmann et al., 2012). The reason for these differences was not evident, but the authors speculated that market penetration, patient preferences, familiarity with brand name, flavorings or other excipients, or even subtle differences in bioavailability could be contributing factors. Only one study to date has compared prevalence of frequent injection (at least weekly) of BUP/NX film with that of BUP/NX tablets (Larance et al., 2014). This Australian study was conducted in 2012, using two distinct samples: (1) out-of-treatment injection drug users (n = 541) and (2) patients in opioid addiction treatment with either buprenorphine or methadone pharmacotherapy (n = 544). It showed no significant differences in either sample in the prevalence of frequent injection of BUP/NX films (out-of-treatment persons: 1%; patients: 3%) compared with BUP/NX tablets (out-of-treatment persons: 3%; patients: 9%). These percentages were similar to the prevalence of frequent methadone injection (4% among out-of-treatment persons; 3% among patients). Frequent injection of BUP was higher (6% among out-of-treatment persons; 11% among patients) than for both BUP/NX formulations.

Reports of buprenorphine injection rates surpassing heroin, methadone, or other full *mu* opioid agonist analgesics

are rare across the world. In the United States, where there is ready availability of full agonist *mu* opioid analgesics (ie, those formulated for treatment of pain) and heroin, buprenorphine was infrequently described as the primary drug of abuse among individuals seeking prescription drug abuse treatment (<3%) (Cicero et al., 2007). However, this has not been the case in all countries such as Finland and Malaysia, where far greater problems of regular buprenorphine injection emerged because of unique circumstances in both countries.

Finland developed significant problems with increasing numbers of daily IV buprenorphine users in the late 1990s when heroin availability was declining because of decreased supply from Afghanistan (National Bureau of Investigation, 2003; Uosukainen et al., 2013c). Finnish authorities reported that the primary source of misused BUP was from outside its borders (Forsell et al., 2010). By 2001, BUP replaced heroin as the most commonly abused opioid among persons seeking addiction treatment (Uosukainen et al., 2013c). Averaged over the 11-year period from 1998 to 2008, 16% of those surveyed who were seeking *any* type of substance abuse treatment identified buprenorphine as their primary drug of abuse; 80% were using it intravenously, and most also were misusing other prescription-type medications (Uosukainen et al., 2013c). Treatment for people who were abusing buprenorphine was primarily with lofexidine and withdrawal protocols, and mortality rates were high, similar to those with primary abuse of heroin (Uosukainen et al., 2013b). Because of the emergence of widespread IV BUP abuse, BUP was restricted for treatment only during pregnancy, and BUP/NX, introduced in 2006, became the more commonly prescribed formulation. Notably, BUP and BUP/NX treatment have stringent criteria for treatment entry that begins in specialty addiction treatment clinics where dosing is observed (Forsell et al., 2010; Uosukainen et al., 2013a).

To evaluate the impact of the introduction of BUP/NX in Finland on prevalence of injection of BUP, a survey queried out-of-treatment needle exchange participants in 2005 (n = 176) and in 2010 (n = 276) (Simojoki and Alho, 2013). Daily injection BUP misuse decreased from 81.7% in 2005 to 74.3% in 2010; however, BUP remained the most commonly abused drug by the IV route. Daily injection use of BUP/NX was reported to be 14.7% in 2010, more than 5-fold lower than daily injection of BUP among these needle exchange participants. Most (64%) of this sample in 2010 endorsed their desire to enter opioid maintenance treatment. Unfortunately, approximately 50% reported not being accepted for treatment. The study authors concluded, in part, that there was a need for more opioid maintenance treatment options in Finland.

In Malaysia, injection of BUP emerged shortly after its introduction in 2002 during a rapid OBOT expansion provided primarily by general practitioners who received no training or practice guidelines for OBOT (Vicknasingam et al., 2010). Moreover, providers received additional income if they dispensed the medication (rather than prescribed) and received higher payment for more medication dispensed. Reports of frequent prescribing and dispensing of weekly-to-monthly take-home supplies of medication ensued. In 2006, one survey reported that among 276 persons recruited with past weekly IV BUP use, 63% were injecting BUP daily, which was most commonly (ie, 76% of reports) received from a private general practice clinic (Vicknasingam et al., 2010). BUP was removed from the Malaysian market in 2006 and replaced with BUP/NX in 2007. A mandatory 8-hour training was introduced and a national registry of patients receiving BUP/NX was created. Shortly after BUP/NX became available in 2007, a survey recruited 204 persons with lifetime BUP/NX IV use. Within this sample, 34% were injecting BUP/NX daily. The top reasons for injecting BUP/NX included to treat addiction (81%), alleviate withdrawal (70%), less expensive than heroin (57%), and for pleasure (36%). The most common source again was private practice general practitioners (77%). The study authors recommended reducing the financial incentives to physicians for dispensing large quantities of BUP/NX (Vicknasingam et al., 2010).

RISK FACTORS FOR IV BUPRENORPHINE MISUSE

The studies earlier show that IV use of BUP is more frequent than BUP/NX, and IV buprenorphine use can occur in any country—a reminder that no particular type of health care system or addiction treatment system is immune. The Finnish experience demonstrates that medications, just like illicit substances (eg, heroin), can become available even if the source is not from within one's own country and suggests that having inadequate access and/or stringently controlled access to opioid maintenance treatment is a potential risk factor for continued diversion and misuse of a therapeutic agent with opioid agonist properties. Attempting but failing to enter OBOT also has been prospectively identified as a risk factor for use of diverted buprenorphine (route not evaluated) in the United States, specifically Appalachia, Kentucky (Lofwall and Havens, 2012), and many barriers to accessing OBOT have been recently documented by the American Society of Addiction Medicine (2013) across the United States. The Malaysian experience, on the contrary, suggests that significant IV buprenorphine use can arise within the context of simply providing buprenorphine in substantial supply (ie, 2–4 weeks) to persons with IV opioid addiction in a treatment setting with provider incentives misaligned with patient treatment needs (eg, payment based on amount of medication dispensed).

Multiple cross-sectional studies have surveyed BUP/NX injectors to explore the reasons underlying their injecting behavior. Reasons commonly (eg, >75%) include self-treatment of withdrawal or addiction, but other reasons are offered, including use for euphoric/pleasurable effects (Alho et al., 2007; Moratti et al., 2010; Vicknasingam et al., 2010; Bazazi et al., 2011); notably, these are not mutually exclusive. Much attention has been given to misuse for reasons that mimic the medical reasons for which the medication is prescribed. These latter reasons should not be used to legitimize IV misuse of diverted medication because many persons addicted to illicit substances (eg, heroin) will similarly report use of heroin to prevent or treat their withdrawal/to feel "normal," and there is clear morbidity and mortality associated with IVDU. There are no data showing that IV self-medication with buprenorphine is effective treatment. Rather, the high percentages of use of diverted medication for "self-treatment" may be a sentinel public health signal that treatment needs are not being

met and that improved access to and/or expansion of treatment are essential.

The evidence base evaluating risk factors for IV use of buprenorphine among persons currently receiving buprenorphine treatment is scant with very few prospective studies. One cross-sectional study in France conducted 404 face-to-face confidential interviews with patients receiving treatment with BUP; only those who used BUP for the first time by physician prescription were eligible (Vidal-Trecan et al., 2003). Multivariable logistic regression demonstrated that having a history of IVDU was the most robust risk factor (odds ratio [OR] = 13.2), followed by current cannabis use (OR = 3.4) and having no salary (OR = 1.6). Ongoing heroin use during OBOT was protective (OR = 0.2), likely because injecting buprenorphine may precipitate withdrawal in regular heroin users, but more importantly, this result suggests that the patient could be trading or selling their medication in exchange for their primary opiate of choice, heroin. Another study from France prospectively evaluated patients in BUP treatment by telephone. The first phone survey was conducted after a minimum of 3 months in OBOT, and the second was conducted 6 months later (Roux et al., 2008). The response rate was 70% (n = 111). Multivariate analysis adjusting for the time since first drug injection (a proxy of drug addiction severity) showed 3 significant risk factors for IV BUP use over the 6-month period: (1) perception of BUP dose as inadequate (OR = 2.7; median dose was 6 mg); (2) history of suicidal attempt or ideation (OR = 2.6); and (3) the number of years of IVDU (OR = 1.05). Injecting is a behavior that is highly conditioned; it is not surprising that such a behavior frequently repeated over months to years would continue for some time after treatment entry. However, it is not yet known what interventions may best extinguish injection behavior. This study also highlighted the role of appropriate dosing and comorbid conditions on risk of IV buprenorphine misuse, which will be discussed in more detail in the recommended practices section.

CONSEQUENCES OF BUPRENORPHINE MISUSE AND DIVERSION

Injection of any drug can cause a host of medical problems from local tissue site injury (eg, tissue necrosis and abscess) to systemic infections such as endocarditis; these are also consequences that have been reported with buprenorphine injection (Gouny et al., 1999; Ho et al., 2009). In addition, pharmaceuticals intended for oral consumption may contain talc and other excipients that, when injected, can cause additional systemic complications, such as pulmonary granulomas (Waller et al., 1980). Reports of uncommon infections such as ocular candidiasis have occurred after removal of buprenorphine from the mouth (while under "supervision") for later injection (Aboltins et al., 2005) and after injecting BUP that has been combined with contaminated solutions (Cassoux et al., 2002). There also have been case reports of severe liver pathology after parenteral use, sometimes involving other hepatotoxins and/or coinfection with hepatitis B and/or C (Berson et al., 2001; Herve et al., 2004).

The most worrisome patient and public health outcome to be associated with any medication is death. Deaths involving buprenorphine have been well described from France, where BUP treatment rapidly grew from 1000 patients in 1994 to 55,000 patients in 1998 (Auriacombe et al., 2001). Outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy is provided there primarily by general practitioners (Auriacombe et al., 2004) who can prescribe BUP to an unlimited number of patients and without any required training. A maximum of 7 days of take-home doses is now recommended (Auriacombe et al., 2004), and although supervised dosing, urine drug testing, and counseling are not required, French pharmacies can and do provide daily supervised dosing if the physician requests this service (Vignau et al., 2001). Surprisingly, buprenorphine maintenance doses were frequently coprescribed (43%) with benzodiazepines (Thirion et al., 2002). Reports of deaths involving BUP followed; decedents frequently had positive toxicology tests for benzodiazepines and signs of injection drug use, suggesting that the concomitant use of benzodiazepines and parenteral administration were risk factors for death (Reynaud et al., 1998; Tracqui et al., 1998). Other countries have also reported buprenorphine-related deaths, most often in the context of concomitant use of benzodiazepines and/or alcohol, highlighting the fact that combined use with nonbenzodiazepine central nervous system depressants is also a risk factor for fatal overdose (Hakkinen et al., 2012; Selden et al., 2012). Death rates attributable to BUP were 3-fold less compared with methadone-related deaths in France over 1994–1998 when adjusted for the number of patients receiving each pharmacotherapy (Auriacombe et al., 2001). Importantly, the number of drug overdose deaths decreased by 79% in France from 1995 through 1999, whereas addiction treatment with BUP and methadone increased by more than 95% and syringe exchange programs were developed (Auriacombe et al., 2004).

In the United States, there are currently approximately 23,000 physicians with a waiver to provide OBOT (28% of those have a 100-patient limit; the remainder have a 30-patient limit; Drug Enforcement Agency National Technical Information Service, 2013). The number of deaths involving sublingual buprenorphine products (including generics) that are specifically approved by the FDA for the indication of opioid dependence treatment from 2002 to October of 2013 totaled 464 (e-mail communication with Reckitt Benckiser Pharmaceuticals). These deaths exclude those involving injectable buprenorphine (ie, Buprenex, n = 5; and nonspecified buprenorphine products, n = 53). Of the 464 deaths, there were 29 perinatal/neonatal deaths (eg, miscarriage and stillbirth) whereby the mother was taking buprenorphine during pregnancy (not known whether the mother was receiving buprenorphine as part of addiction treatment), 6 infant deaths, and 3 noninfant pediatric deaths; 423 deaths (91%) involved BUP/NX and 41 (9%) involved BUP. These results should not be interpreted to indicate that BUP/NX is less safe than BUP because BUP/NX has been more widely prescribed than BUP, and, unfortunately, many of these deaths (n = 238) were reported to Reckitt Benckiser Pharmaceuticals without an assessment of the causality/role of buprenorphine in the death. It also is not known what proportion involved the use of benzodiazepines or other central nervous system depressants. However, one way to attempt to control for availability in calculation of death rates of BUP/NX versus BUP is to calculate

patient-treatment years (PTY) by assuming an average dose of 16 mg/d per patient based on amount of product sold (from 2003 for Suboxone and Subutex tablets and from September 2010 for Suboxone film to September 2013; data not available for the generic products). Calculations from Reckitt Benckiser Pharmaceuticals show that there have been 1,510,109 PTY for Suboxone (ie, 981,056 PTY for Suboxone tablets and 529,053 PTY for Suboxone film) and 30,701 PTY for Subutex tablets. Thus, exposure to Suboxone products is 49-fold higher than to Subutex tablets, suggesting that the finding of 10-fold higher proportion of deaths involving BUP/NX than BUP is actually lower than expected, although this is not conclusive because the number of deaths included generic product, whereas calculations of PTY excluded generics. It is critical to remember, too, that morbidity and mortality among untreated opioid-dependent persons, including fetuses and neonates of pregnant women, is higher than that in the general population without substance abuse (eg, Alroomi et al., 1988; Hulse et al., 1998; Neumark et al., 2000). For example, among pregnant, opioid-dependent women, other comorbid substance use, social situations (eg, domestic violence and problems accessing prenatal care), and medical (eg, infections) and psychiatric problems can all adversely impact fetal and neonatal outcomes (eg, Ludlow et al., 2004; Jones and Kaltenbach, 2013). For instance, most pregnant, opioid-dependent women (∼90%) smoke cigarettes (eg, Tuten et al., 2003; Quigley et al., 2013), and cigarette smoking is an independent risk factor for spontaneous abortion, stillbirths, and sudden infant death syndrome (Rogers, 2008). Recommendations for improvement in substance-involved death data collection systems are listed in Table 1.

Although the number of buprenorphine-related deaths are likely underestimated because coroners are/were not routinely testing for buprenorphine, the number of deaths involving full *mu* agonist opioid analgesics is markedly higher. For instance, in the year 2008, the Centers for Disease Control and Prevention reported 14,800 deaths due to prescription opioid analgesics, and there is no evidence that deaths involving this class of medication are declining.

There also have been increasing reports of pediatric exposures to buprenorphine (Boyer et al., 2010; Martin and Rocque, 2011; Pedapati and Bateman, 2011). The Centers for Disease Control and Prevention (www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a5.htm) reports that BUP/NX "caused 9.5% of emergency hospitalizations for drug ingestion by children less than 6 years, a greater proportion than any other single medication, even though in 2009 buprenorphine products amounted to only 2.2% of all retail opioid prescriptions and 0.16% of all retail prescriptions." Although the Centers for Disease Control and Prevention did not differentiate between BUP/NX tablet and film exposures, a recent study reported significantly lower rates of unintentional exposures to BUP/NX film among children aged 28 days to 6 years than that for BUP/NX tablet and BUP (Lavonas et al., 2013). It is important for all patients receiving buprenorphine to understand that ingestion of buprenorphine, even without other medications, can be deadly in children; the reported ceiling effects on respiratory depression in adults do not seem to apply to children (Kim et al., 2012). Unintentional exposures to children should be preventable. Physicians should discuss the necessity of safe storage with all patients because the source of medication ingested can be from family and friends, who may not have children themselves.

Overall, the safety profile of buprenorphine in the United States seems superior to that of methadone with 2- to 3-fold lower rates of drug diversion reports and poison center calls than methadone (Dasgupta et al., 2010). Also, similar to France, recent data reveal a significant relationship between a decline in heroin overdose deaths after the approval and implementation of buprenorphine into the treatment system in Baltimore City, an area of the United States with particularly high rates of heroin abuse and heroin-related deaths (Schwartz et al., 2013).

In addition, the finding that benzodiazepines are most commonly associated with deaths related to buprenorphine, similar to their presence also in heroin, methadone, and full *mu* opioid agonist prescription analgesic-related deaths, demonstrates that the respiratory depressant effects of buprenorphine are increased in the presence of benzodiazepines and alcohol, as supported by mechanistic preclinical studies (eg, Gueye et al., 2002; Pirnay et al., 2008 and others). Thus, benzodiazepine availability (and coprescribing), diversion, and

TABLE 1. Ongoing Clinical Research Needs

Develop sensitive and specific clinical methods for detecting misuse and diversion while in treatment
Develop efficacious prevention techniques and therapeutic responses to diversion and misuse that do not adversely affect treatment access or erode treatment benefits
Evaluate impact of public policy, including insurer and provider incentives and/or punishments that may inadvertently promote misuse and diversion and prevent therapeutic responses (eg, limitations on the number of provider visits, US Drug Enforcement Agency regulations that do not allow for a OBOT provider to store a patient's prescription medication once dispensed to patient, even if for purpose of supervised dosing at OBOT clinic)
Quantify amount of off-label prescribing of buprenorphine for pain and its relationship to diversion and misuse
Determine impact of product packaging on diversion and misuse and pediatric exposures
Continue drug development and consider alternative pharmaceutical abuse deterrents (eg, higher naloxone to buprenorphine ratios, alternative abuse deterrent formulations, depot formulations)
Improve fatal substance overdose data collection systems to ensure comprehensive assessment of all substances present at the time of death, including both controlled and uncontrolled substances (commonly prescribed noncontrolled substances may also contribute to fatal outcomes [eg, antihypertensives and antipsychotics]); clarify whether involved substances were prescribed or not prescribed (indicating diversion) to decedents; and include whether there is evidence of new or long-term use of each substance. This information could be used to learn how prescribing practices and patient use patterns of prescribed or diverted substances contribute to overdose mortality and aid in the development of targeted interventions

OBOT, outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy.

misuse warrant increased attention from the medical, scientific, and public policy makers because this drug class is contributing to public health harms. During the introduction of buprenorphine in France, a significant problem with concomitant benzodiazepine abuse arose with flunitrazepam, specifically. In response, the French Drug Agency modified the regulation of flunitrazepam to limit its prescription and dispensing and its abuse decreased. However, this was followed by a rise in abuse of clonazepam until its regulatory control was tightened in 2010, limiting its prescription to a maximum of 4 weeks as a hypnotic agent and 12 weeks as an anxiolytic (Frauger et al., 2013).

RECOMMENDED PRACTICE BEHAVIORS TO DETER MISUSE AND DIVERSION

There are several published practice guidelines and recommendations for OBOT in the United States, yet most have a very limited or no discussion about how to evaluate diversion and misuse of buprenorphine clinically nor do they provide strategies for screening, monitoring, or responding to these behaviors specifically within the outpatient setting of OBOT (Center for Substance Abuse Treatment, 2004, 2005; Fiellin et al., 2004; Kosten and Fiellin, 2004; Kraus et al., 2011; www.fsmb.org/pdf/2013_model_policy_treatment_opioid_addiction.pdf, and http://pcssmat.org/wp-site/wp-content/uploads/2014/02/PCSS-MAT GuidanceAdherence-diversion-bup.Martin.pdf). This may be due, in part, to a lack of controlled studies that examine interventions to screen, monitor, and reduce medication misuse and diversion. Moreover, there may be concern that, if these behaviors are acknowledged as occurring within US OBOT, it will result in burdensome regulations, such as mandatory supervised dosing for all patients, as increased regulation has been a common response to diversion historically (Bell, 2010; Jaffe and O'Keeffe, 2003), or more extreme measures such as revocation of Drug Abuse Treatment Act of 2000 or the rescheduling of buprenorphine to Schedule II (which would functionally preclude its use in OBOT). The goal here is to remind practitioners why diversion and misuse are deserving of clinical attention and to provide clinical recommendations for detecting, evaluating, and responding therapeutically to these behaviors to retain patients in treatment and assist them in making positive changes in their recovery. Most of the clinical practices described are informed by basic principles of behavior analysis, addiction medicine, and addiction psychiatry.

From the earlier discussion, it is clear that medication misuse and diversion are common behaviors and when they occur within treatment, they indicate medication nonadherence. Nonadherence decreases treatment effectiveness (for all medical disorders) and is associated with relapse to illicit opioid use within OBOT (Tkacz et al., 2012). If one is interested in decreasing relapse, one must become interested also in medication adherence. Thus, assessment for misuse and diversion is recommended at each clinical visit, with placement of these behaviors on patients' problem list so that they can be addressed therapeutically, rather than punitively.

A punitive "no tolerance" approach with automatic discharge from treatment is highly unlikely to help patients, because untreated opioid addiction is characterized by relapse (continued use of illicit [ie, diverted] opioids is the norm) and increased morbidity and mortality (McLellan et al., 2000). Good treatment benefits both individual and public health even when patients are unable to achieve continuous drug abstinence and cessation from all criminal activity and IVDU (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998; Carrieri et al., 2006). For example, a recent study compared 3 groups of injection drug users receiving needle exchange services in Norway: (1) persons currently in addiction treatment with methadone or buprenorphine (n = 341), (2) persons with no prior treatment with these medications (n = 1063), and (3) persons who had prior, but not current, treatment with these medications (n = 356). Those currently in treatment, despite continued IVDU, had significantly fewer nonfatal overdoses (OR = 0.5), committed fewer thefts (OR = 0.6), and reported dealing drugs (OR = 0.7) less often in the prior month. They were also less likely to use heroin daily or near daily (OR = 0.3) than the other groups that were not in treatment (Gjersing and Bretteville-Jensen, 2013). This does not imply that physicians must accept and do nothing about medication misuse and diversion or that they should continue to prescribe buprenorphine to patients who are distributing it to others rather than taking it themselves. Rather, the point is that treatment can be beneficial even if the ideal outcome is not attained (eg, 100% medication adherence and abstinence from all substances of abuse). The goal is to evaluate treatment benefits and harms for each patient, individualizing the treatment plan to minimize harms without adversely affecting the benefits provided.

Reasons for buprenorphine diversion and misuse while in OBOT are listed in Table 2. Once providers understand the context and circumstances around these behaviors, practical solutions can be formulated. For instance, for patients who

TABLE 2. Patient Reasons for Medication Diversion and Misuse While in OBOT

Reasons for Diversion	Reasons for Misuse
Peer pressure (eg, expectation that medication is shared, may be facilitated by excessively high daily doses and large supplies)	Habit (eg, history of IV or intranasal drug use increases risk of injecting or snorting medication, respectively)
Help addicted friend or family member	Perceived underdosing
Make money (eg, pay off bad debt, pay for living expenses/medical fees, to buy preferred opioid for misuse)	Relieve opioid withdrawal, craving, and/or treat addiction
	Achieve positive effects (eg, get high, increased energy)
	Relieve negative states (eg, pain, anxiety, depression)

IV, intravenous; OBOT, outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy.

encounter drug dealers every month at the pharmacy where they fill their prescription and are pressured to sell their medication, a recommendation to change pharmacies and assistance with finding financial help may be welcome if the medication is being sold to pay off old debts. For patients unable to escape from drug-addicted social networks, it may be helpful to discuss the option of maintaining a secretive status regarding having medication (Havnes et al., 2013).

Patients may not disclose medication misuse and diversion; however, some clinical practice behaviors (see Table 3), such as monitoring urine drug test outcomes, including for buprenorphine, are recommended and may be helpful. Inexpensive Clinical Laboratory Improvement Amendments (CLIA) waived urine tests for buprenorphine are now readily available in the United States. In a cross-sectional study in India, 14% and 34% of patients receiving BUP/NX and BUP, respectively, tested negative for buprenorphine on random observed urine testing (Balhara and Jain, 2012). A test result that is positive for buprenorphine but negative for its primary metabolite, norbuprenorphine, would also be incongruent with daily medication use. Admittedly, urine drug testing has limited practical use in detecting intermittent nonadherence because of the long half-life of buprenorphine, as patients could skip medication for several days and still produce a urine screen positive for buprenorphine. State prescription-monitoring reports are useful in detecting multiple buprenorphine prescribers simultaneously (eg, doctor shopping) and receipt of other controlled substances. Random medication counts can also be done at the physician office or at the pharmacy to screen for potential diversion and misuse (Lofwall et al., 2010), although there are no data on the sensitivity or specificity of this approach. It is noteworthy that each individually packaged BUP/NX film product in the United States contains a unique 10-digit identity number and quick response code that could be scanned at any point in the chain of medication distribution. Although this tracking technology is not being used currently, it has the potential to trace medication found on the street back to the dispensing pharmacy, physician prescriber, and patient recipient. This could be helpful for providers and patients if used therapeutically in treatment but could be harmful if it became a law enforcement tool used primarily to punish providers and patients.

Outpatient opioid addiction treatment with sublingual buprenorphine pharmacotherapy providers may want to consider how their practice, which should be composed of numerous components (see Fig. 1), can help minimize and respond to misuse and diversion when it occurs. To prevent attracting individuals who are seeking medication to sell on the street, the OBOT provider can make it clear at the time of scheduling the initial appointment that there are multiple aspects of treatment (eg, assessment and monitoring), and frequent visits until stable. Providers may choose to explain that longer supplies of medication will be provided with increasing objective evidence of stability. This is a practical example of integrating contingency management into clinical practice. Contingency management is a highly effective behavioral therapy that uses positive reinforcers (eg, longer duration of prescription or less-frequent appointments) to encourage and promote desired behavioral changes, such as adherence and drug abstinence (Stitzer and Vandrey, 2008; Gerra et al., 2011). To avoid unintentional diversion (and pediatric exposures) from patients' prescription buprenorphine at home, all OBOT patients could be advised on safe storage practices (eg, in a lock box and not in kitchens and bathrooms or other common areas where it could be easily "borrowed" or stolen). Use of the combined BUP/NX versus BUP formulation should be preferred for nonpregnant patients, given its relative lower abuse liability. However, clinicians may be presented with pleas by patients for prescription of BUP over BUP/NX if generic BUP is significantly less expensive than BUP/NX, particularly for patients without health insurance. Such cases require a careful individual assessment and documentation of the individual risks and benefits of prescribing the formulation without naloxone (eg, Is no treatment the alternative? Is this a high-risk patient for IV misuse because history of IVDU?), including a plan for monitoring and switching to product with naloxone should concerns about diversion and misuse arise. Therapeutic dosing and prescribing are also important. The FDA package insert for BUP/NX states that the upper recommended dose is 24 mg/d. Dosing more than 24 mg/d is off-label; physicians

TABLE 3. Checklist to Help Detect Diversion and Misuse While in OBOT

Practice Behavior	Explanation/Examples
Talk	Define diversion and misuse with each patient, ask for patient to give examples of each from their experience with illicit drug use, discuss potential triggers for each patient, develop strategies to combat these behaviors, follow up at each visit about occurrences or close calls of medication diversion and misuse just as with use of illicit opioid of choice; discuss openly throughout treatment
Examine	Nonhealing or fresh track marks or intranasal erythema may indicate buprenorphine injection or intranasal use, respectively, or that other substances are being misused whereby the medication could be sold/traded for the opioid of choice. Lack of objective signs of opioid withdrawal despite ongoing patient report of severe withdrawal
Listen	Repeated requests for early refills because of various reasons (lost, stolen, or washed [forgot to take out of clothing] medications)
Monitor	Missing appointments, incorrect medication tablet/film counts, urine tests with absence of buprenorphine and/or norbuprenorphine, unexpected medical problems for a patient believed to be in recovery (eg, abscesses), state prescription monitoring reports showing ongoing receipt of prescription opioids or other controlled substances that the patient denied being prescribed and/or multiple prescriptions from different OBOT providers over the same period of time
Collaborate	Feedback from pharmacist about unusual behavior from patient, such as appearing intoxicated or being accompanied by someone who seems to be overly interested in the medication, exchange of something in parking lot or in waiting area. Counselor and family members who are not currently addicted and who have patients' best interest in mind report patient contact with old drug-using friends or nonadherence with medication if they are supervising ingestion

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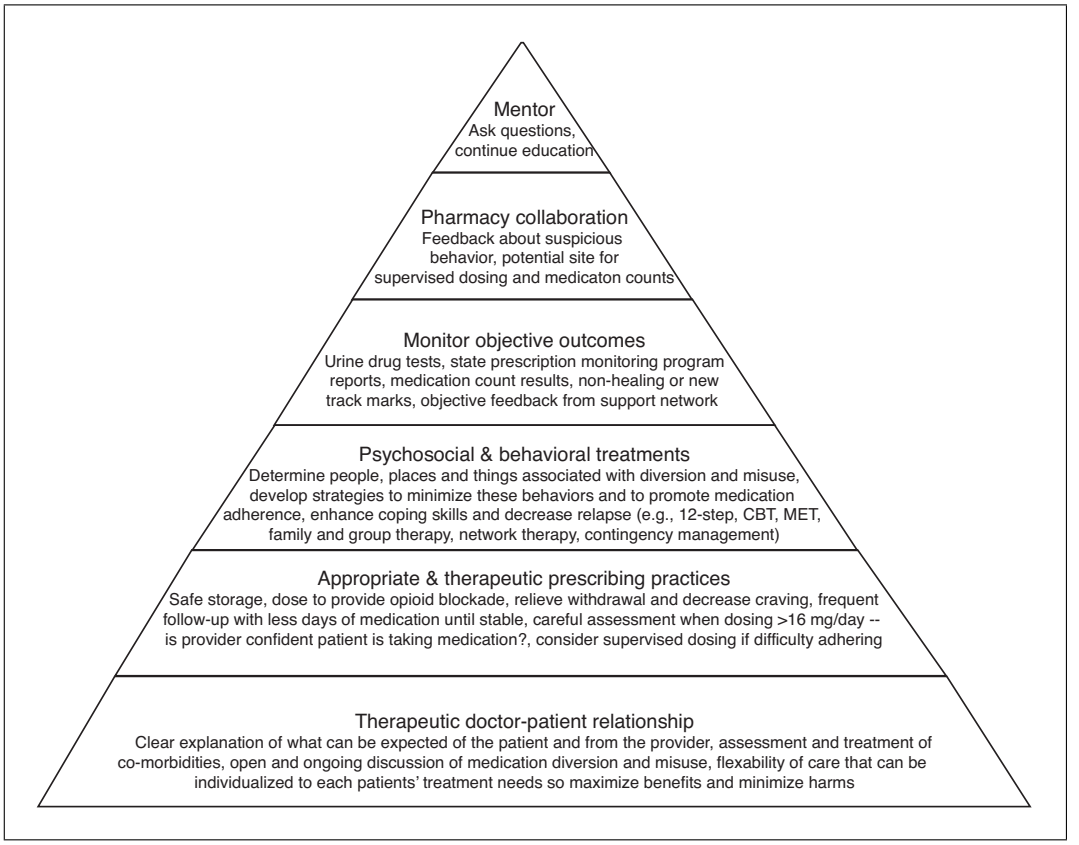

FIGURE 1. Components of outpatient opioid dependence treatment. A detailed explanation of the practices detailed in this figure can be viewed online at http://www.cecentral.com/buprecme (Lofwall et al., 2011).

should document a rationale for surpassing this dosage, including showing that lower daily doses were not adequate. There are no studies to date showing that doses higher than 24 mg/d produce superior results compared with 24 mg/d. Most patients will stabilize on doses between 8 and 24 mg daily. Dosing should be flexible and incremental, according to published practice guidelines. Therapeutic dosing must take into account both the evidence base and the individual patient response to medication, in order for dosing and the overall treatment plan to be tailored to each individual patient. Providers should avoid (1) subtherapeutic dosing (eg, inadequate opioid blockade [ie, ability to still get high or have good effects from illicit opioid use while taking the prescribed buprenorphine dose] or inadequate withdrawal suppression), (2) supratherapeutic dosing (which may allow patient to maintain stability while sharing or selling a portion of their medication), and (3) providing large drug supplies to unstable patients (eg, several weeks or more), which can increase risk and provide opportunity for diversion and misuse.

When diversion and misuse are suspected or confirmed, potential responses include practical solutions individualized to the particular patient situation that were discussed earlier (if known), but also include more frequent clinic and/or counseling visits, smaller supplies of unsupervised medication (eg, 1-week supply or less), and initiation of or increase in the frequency of supervised medication ingestion. Thrice-weekly dosing of buprenorphine under supervision is an effective treatment strategy that reduces clinic burden without compromising patient treatment outcomes compared with daily dosing under supervision (Bickel et al., 1999; Amass et al., 2001; Marsch et al., 2005). Observed ingestion at the OBOT clinic, pharmacy (more common outside the United States), or by a trusted non–drug-using support that lives with or nearby the patient is another strategy to consider. For example, network therapy encourages patients to enlist non–drug-using supports in their treatment who can monitor medication ingestion. Network therapy has been shown to increase opioid abstinence significantly among heroin-dependent adults in OBOT (50%) compared with standard medication management with counseling (23%) (Galanter et al., 2004). However, it is critical to avoid choosing support members with an abusive or exploitative relationship with the patient.

It is important to remember that supervised dosing does not eliminate diversion and misuse, as highlighted earlier with the Australian experience. Liquid methadone and buprenorphine tablets can be held in cheeks and taken out of the mouth among patients motivated to misuse and divert if there is a brief lapse in supervision (eg, supervisor turns around for a moment and/or lack of mouth check). A recent comparison between the BUP/NX tablet and film product suggests that supervision may be more effective with the film because it dissolves more quickly and is more mucoadhesive (ie, stickier)

than the tablet, making it difficult to remove from the mouth (Lintzeris et al., 2013). However, a recent study showed that under "supervision," doses of medication for opioid addiction treatment were removed among patients dispensed BUP/NX tablet (19%) and BUP/NX film (20%) (Larance et al., 2014). It is not clear whether patients were able to slip medication from hand to pocket because of medication not being placed directly into the patient's mouth or whether there were other strategies (eg, dry mouth and overlapping films that may decrease effective mucoadhesion). Notably, in this study, among patients receiving supervised BUP/NX film dosing, 43% reported that more than 3 films were placed in their mouth at once, suggesting that overlap of films may have played a role.

Daily supervised dosing as a regulatory requirement for all patients may pose a barrier to treatment entry for patients, limit further treatment expansion (eg, increased costs and requirements for storing and dispensing controlled drug from a clinic), and exacerbate the problems of untreated addiction. It is possible, however, that supervised dosing may be helpful in circumstances where patients do not have safe storage options (eg, homeless) or would benefit from the increased structure and clinic contact that supervised dosing can provide. Although limited data exist on the frequency of supervised dosing and treatment outcomes, one randomized controlled study showed that thrice-weekly versus once-weekly supervised buprenorphine dosing in OBOT produced only modest decreases in patient treatment satisfaction and no differences in treatment retention, opioid use, or medication adherence (Fiellin et al., 2006; Barry et al., 2007). Some patients may require an alternative treatment setting or pharmacotherapy, such as methadone (Kakko et al., 2007). Improving linkages between practices and providers, which vary in their intensity and setting, are necessary for flexible and uninterrupted quality care.

CONCLUSIONS

Overall, buprenorphine diversion and misuse seem to be common behaviors of opioid-addicted individuals, whereby the frequency of use of diverted medication, route of misuse, and subsequent harms are influenced by various factors. These factors include the pharmacological profile of the particular buprenorphine formulations, physical dependence status of the individual, individual experience with route of drug use, availability of buprenorphine or alternative opioids in the environment, and public policies within and surrounding geographic areas regarding opioid addiction treatment services. Table 1 suggests areas for future clinical research where current gaps in knowledge exist. Unfortunately, deaths involving buprenorphine have occurred around the globe, most commonly in combination with central nervous system depressants, and in the United States, deaths involving buprenorphine are far fewer in number than deaths involving methadone and other full *mu* opioid agonist prescription analgesics. Importantly, epidemiological data from France and the United States showed that with OBOT expansion, there was an overall decrease in drug overdose deaths. Thus, any steps taken to minimize buprenorphine diversion and misuse must be careful not to undermine the positive patient and public health benefits gained from expanded treatment access.

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