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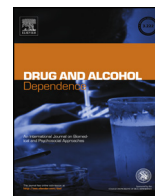


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Factors contributing to the rise of buprenorphine misuse: 2008–2013



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ABSTRACT

Objective: The purpose of the present study was to examine the motivations underlying the use of buprenorphine outside of therapeutic channels and the factors that might account for the reported rapid increase in buprenorphine misuse in recent years.

Methods: This study used: (1) a mixed methods approach consisting of a structured, self-administered survey ($N=10,568$) and reflexive, qualitative interviews ($N=208$) among patients entering substance abuse treatment programs for opioid dependence across the country, centered on opioid misuse patterns and related behaviors; and (2) interviews with 30 law enforcement agencies nationwide about primary diverted drugs in their jurisdictions.

Results: Our results demonstrate that the misuse of buprenorphine has increased substantially in the last 5 years, particularly amongst past month heroin users. Our quantitative and qualitative data suggest that the recent increases in buprenorphine misuse are due primarily to the fact that it serves a variety of functions for the opioid-abusing population: to get high, manage withdrawal sickness, as a substitute for more preferred drugs, to treat pain, manage psychiatric issues and as a self-directed effort to wean themselves off opioids.

Conclusion: The non-therapeutic use of buprenorphine has risen dramatically in the past five years, particularly in those who also use heroin. However, it appears that buprenorphine is rarely preferred for its inherent euphoric properties, but rather serves as a substitute for other drugs, particularly heroin, or as a drug used, preferable to methadone, to self-medicate withdrawal sickness or wean off opioids.

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1. Introduction

Buprenorphine is a dose-dependent, mixed opioid agonist/antagonist with very high affinity for the mu-opioid receptor, but with limited intrinsic activity compared to other, more commonly used opioid analgesics (Walsh et al., 1994). Moreover, it has a very low dissociation constant from the opioid receptor, generating a very long half-life and limiting dosing frequency (Bickel et al., 1988; Donaher and Welsh, 2006; Greenwald et al., 2003). These properties have made this drug a particularly attractive agent for opioid substitution therapy programs across the world (Donaher and Welsh, 2006; Johnson et al., 1992; Ling et al., 1998; Fiellin and O'Connor, 2002; Degenhardt et al., 2009; Bell et al., 2009; Sullivan et al., 2008; Alford et al., 2011). While it is maintained that these programs have been successful in reducing use of illicit opioids, buprenorphine itself has become a leading drug of choice for

non-therapeutic purposes (e.g., produce euphoria/get high) in many countries which have such programs (Bell, 2010; Auriacombe et al., 2004; Carrieri et al., 2006; Aalto et al., 2007; Yokell et al., 2011; Guichard et al., 2003; Vidal-Trecañ et al., 2003; Lavonas et al., 2014).

Recognizing this fact, the manufacturer reformulated buprenorphine with low doses of naloxone prior to its release in the United States for opioid treatment (Reckitt Benckiser Pharmaceuticals Inc., 2014). It was assumed that naloxone would antagonize the euphoric properties of buprenorphine, or precipitate withdrawal in opioid tolerant individuals (Chiang et al., 2003; Mendelson and Jones, 2003; Walsh and Eisenberg, 2003; Stoller et al., 2001). Thus, its risk of misuse was considered to be quite low (Mammen and Bell, 2009; Alho et al., 2007; Comer et al., 2010; Schuster, 2006). Based on early assessments of the drug, the Food and Drug Administration not only approved buprenorphine and buprenorphine/naloxone as part of comprehensive opioid harm reduction program in 2002, but there was sufficient confidence with these drugs that they were approved to be prescribed for home use rather than made available only in stand-alone methadone clinics, which are inconvenient, carry a significant social stigma, and use an inherently less safe

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opioid (methadone) with significant adverse side-effects (Peterson et al., 2010; Schwartz et al., 2008; Zaller et al., 2009). However, given the experience in Europe, the FDA was cautious in its approach, requiring specialized training and limitations of 30 buprenorphine patients at one time for physicians (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014; Drug Addiction Treatment Act of, 2000; Center for Substance Abuse Treatment (CSAT), 2004). With the early apparent success of these programs, restrictions were lifted in 2006 such that up to 100 patients could be treated by an individual physician. Additionally, the introduction of less expensive generics in 2009 further contributed to large increases in buprenorphine prescriptions in the past five years (Drug Enforcement Administration, 2009). As expected from earlier work showing a direct link between the extent of therapeutic exposure and diversion for non-therapeutic purposes (Cicero et al., 2007a,b), there have been reports of an increase in the diversion and misuse of buprenorphine (Drug Enforcement Administration, 2009; Substance Abuse and Mental Health Services Administration and Drug Abuse Warning Network (DAWN), 2011; United States Department of Justice and National Drug Intelligence Center (NDIC), 2011; Wish et al., 2012).

The purpose of the present study was to examine multiple factors that might account for the rapid increase in buprenorphine misuse in recent years and the motivations underlying the use of buprenorphine outside of therapeutic channels. To address this issue, we used a mixed methods approach utilizing data from structured, self-administered surveys ($N=10,568$) and reflexive, qualitative interviews ($N=208$) among patients entering substance abuse treatment programs across the U.S. with a primary (DSM-IV) diagnosis of opioid dependence. To assess diversion, data were analyzed from semi-structured interviews among a sample of drug-diversion law enforcement units across the country ($N=30$).

2. Methods

This report utilized data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System, a comprehensive series of programs that collect and analyze post-marketing data on the misuse and diversion of prescription opioid analgesics and heroin (Cicero et al., 2007a,b).

2.1. Study Sample 1: SKIP

The Survey of Key Informants' Patients (SKIP) Program consists of over 150 public and privately funded treatment centers (Key Informants), balanced geographically with coverage in 48 states, that recruit patients/clients entering treatment to complete an anonymous survey centered on opioid misuse patterns and related behaviors. Subjects must be 18 years or older and meet DSM-IV criteria for substance abuse with a primary drug that is an opioid (prescription or heroin). Surveys, received on a rolling basis throughout the analyzed period, were identified by a unique case number and sent directly to Washington University in St. Louis (WUSTL) by the respondent. Participants were compensated with a \$20 Wal-Mart gift card. Surveys were categorized by half-year and quarter, with SKIP data for this study analyzed from January 1st, 2008 to September 30th, 2013.

2.2. Study Sample 2: RAPID

To supplement and add context to the structured SKIP survey, a sub-set of patients indicated, by a mail-in postcard provided with the SKIP survey, their willingness to give up their anonymity and participate in an unstructured interview-based study, dubbed Researchers and Participants Interacting Directly (RAPID). During the fourth quarter of 2013, 208 treatment clients consented to participate in a self-administered internet questionnaire via SurveyMonkey. Those participants who indicated prior experience with buprenorphine were re-contacted to further describe their opinions and experiences with buprenorphine $N=(106)$. All participants in the RAPID program were compensated with a \$20 Wal-Mart gift card. Study protocols for the SKIP and RAPID programs were approved by the WUSTL institutional review board.

2.3. Study Sample 3: Drug diversion

The Drug Diversion program of the RADARS® System collects data from a national sample of law enforcement and regulatory agencies with agents assigned to prescription drug diversion investigations. The program includes approximately

260 investigators in 49 states. For this study, thirty investigators participating in the Drug Diversion program in the second quarter of 2013 were randomly selected to participate in a one-time, semi-structured telephone interview. These investigators represented 23 states and were asked general questions about their units, caseload information, primary sources of diversion and primary diverted drugs in their jurisdictions. The study was deemed exempt by the institutional review board at Nova Southeastern University.

2.4. Data analysis

Both SKIP and RAPID programs gather socio-demographic variables (e.g., sex, current age and race/ethnicity). In addition, SKIP and RAPID participants identified their primary drug (e.g., the drug used to get high most frequently in the month prior to treatment), with SKIP respondents asked to also identify all opioid compounds used to get high in the month prior to treatment stratified by formulation and product, including whether or not each product was injected. "Misuse" is used throughout this report to reference both non-therapeutic use and use outside of legal therapeutic channels. Except where noted, SKIP analyses included the entire sample of both heroin and prescription opioid users due to the fact that there was high concurrent use of both drugs; 85% of heroin users also indicated the past month misuse of prescription opioids.

RAPID interview responses to the question "Please briefly explain in your own words the reasons you took buprenorphine or how buprenorphine affected you," were dual-reviewed, and using the principles of thematic analysis, 13 motivations for using buprenorphine were identified. In order to get a more accurate account of the variability in other buprenorphine-related motivations, a series of true/false questions was developed based on eleven identified motivations, with "to get high" and "to treat/prevent withdrawal sickness" excluded because they were asked directly through other SKIP and RAPID questions. Other RAPID data reported in this study were based on direct questions, with participants asked to explain their responses in an open-ended format.

The Drug Diversion program analyzed the responses of law enforcement investigators interviewed about the most commonly diverted prescription drugs in their area. In addition to identifying specific drugs, a review of the interview responses led to the identification of other topics of interest. Topics noted by at least three interviewees were then developed into themes and the presence of a theme (Y/N) was coded back to the interviews. Qualitative data from the Drug Diversion and RAPID programs were reviewed and coded using NVivo version 9. Quantitative data in both SKIP and RAPID datasets were analyzed using IBM SPSS Statistics v21.

3. Results

3.1. Demographics

Table 1 summarizes the gross demographic features of those participating in the SKIP ($N=10,568$; mean N per quarter = 449.1 ± 36.6 SE) and RAPID ($N=208$) programs. As can be seen, the RAPID subset, though much smaller, was quite similar to the larger SKIP sample. The majority of respondents were white and in

Table 1
Comparison of SKIP and RAPID demographic data.

	SKIP ¹ ($n=10,568$)	RAPID ² ($n=208$)
Gender		
Male	50.4	48.4
Average age (\pm SEM)	34.2 ± 0.11	34.9 ± 0.81
Race/ethnicity		
White	78.4	86.4
African American	9.0	4.3
Latino	4.9	3.7
Other	7.7	5.6
Primary drug		
Buprenorphine	1.6	0.7
Fentanyl	1.0	2.0
Heroin	29.8	36.2
Hydrocodone	19.7	20.4
Hydromorphone	3.8	1.3
Methadone	5.6	2.0
Morphine	4.0	3.3
Oxycodone	32.4	29.6
Oxymorphone	1.1	1.3
Tapentadol	0.0	0.0
Tramadol	1.1	3.3

¹ Data collected from January 1, 2008–September 30, 2013.

² Data collected from October 1, 2013–December 31, 2013.

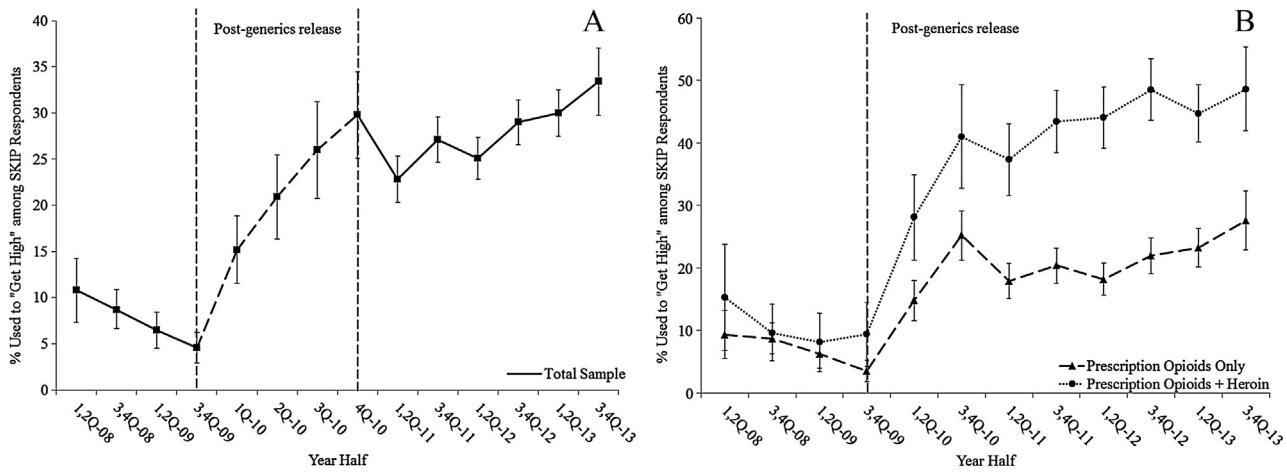


Fig. 1. The percent (95% CI) of the total SKIP sample (A) who used buprenorphine in the past month to get high as a function of half-year intervals from 2008 to the end of 2013. The year following the release of generics (dashed lines) is expressed in quarter-year intervals to emphasize the steepness in the rate of increase; (B) shows the misuse (95% CI) of buprenorphine in those SKIP respondents who used other prescription opioids to get high versus those who used other prescription opioids and heroin. Due to the fact that 85% of heroin users also used prescription opioids, the Ns for those using only heroin were too small (<35) for meaningful analysis.

their early thirties at the time of survey completion, with an even distribution of males and females. Heroin and oxycodone were the most popular primary drugs (i.e., the drug used most often in the past month) in both groups, with buprenorphine one of the least preferred.

3.2. Buprenorphine misuse

Although buprenorphine was endorsed as a primary drug by less than 2 percent of each sample (Table 1), as shown in Fig. 1A the number of SKIP respondents who indicated past month use of buprenorphine to get high was much higher and the rate almost quadrupled from 2008 to 2013. Most notably, there was a steep increase in every quarter of 2010 (detailed in Fig. 1A), the year following the introduction of buprenorphine generics in 2009. Data from law enforcement agents charged with investigating pharmaceutical diversion also indicated that buprenorphine was a significant problem in 2013. It was the fourth most commonly diverted prescription drug as determined by case reports; oxycodone was mentioned by 96.7% of respondents, followed by hydrocodone (80%), alprazolam (57%), buprenorphine (33%) and methadone (30%).

3.3. Heroin

As shown in Fig. 1B, those respondents who used both heroin and other prescription opioids to get high in the past month also misused buprenorphine at rates twice that reported by those only using prescription opioids. Moreover, as shown in Fig. 2A, increases in heroin use paralleled the increase in buprenorphine misuse, most notably in the years following the introduction of a tamper-resistant formulation of OxyContin® in the second half of 2010. Forty percent of drug diversion investigators (N= 12) also noted a parallel increase in heroin and buprenorphine use:

We've seen an increase in heroin and suboxone, they are often packaged together. Suboxone is being prescribed in huge amounts, this girl had 24 refills on her and she was dealing . . . we arrested her shooting up in a restaurant.

3.4. Methadone

As shown in Fig. 2B, as the past month misuse of buprenorphine increased over time, methadone misuse declined, such that, two years after the introduction of buprenorphine generics, methadone was less commonly misused than buprenorphine. In this context,

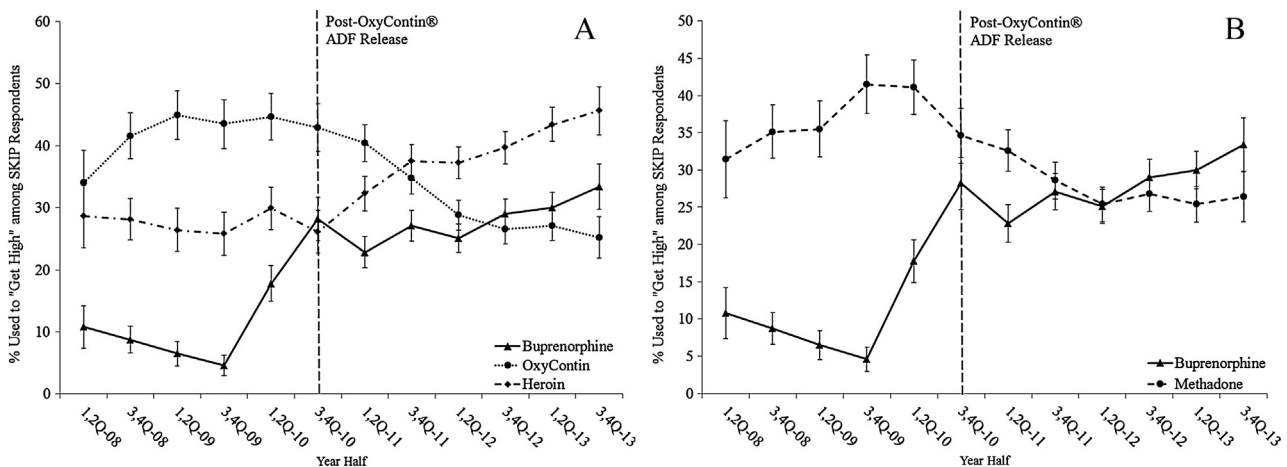


Fig. 2. The percent(95% CI) of the total SKIP sample that used buprenorphine, OxyContin® and/or heroin to get high in the past month plotted as a function of half-year intervals from 2008 to 2013 (A); (B) shows the percent (95% CI) of the total SKIP sample that used buprenorphine and/or methadone to get high in the past month. The introduction of an abuse deterrent formulation of OxyContin® is denoted by the dashed vertical line.

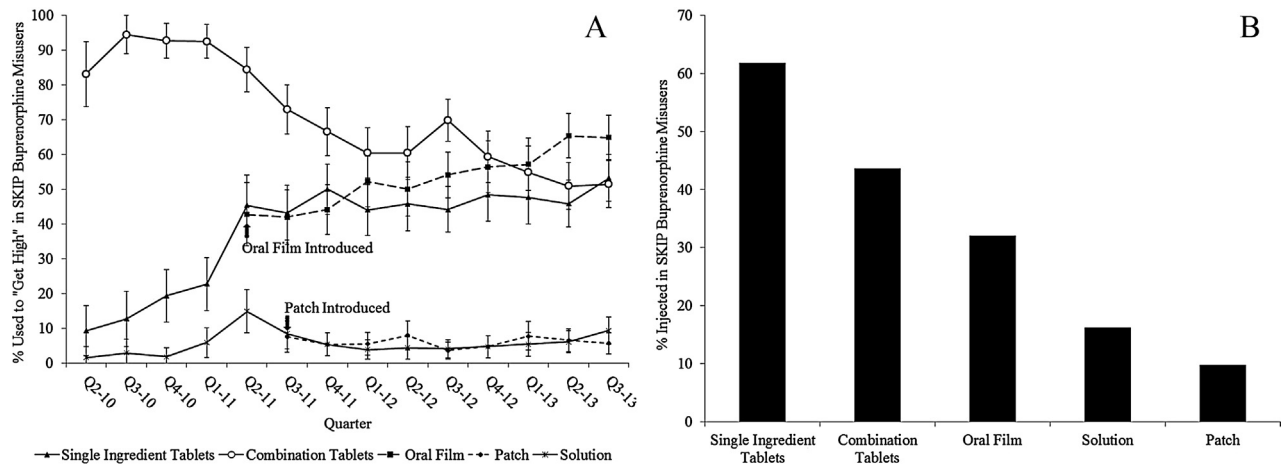


Fig. 3. Buprenorphine product formulations used by SKIP respondents indicating any past month use of buprenorphine to get high plotted as a function of quarter-year intervals (95% CI) (A); (B) shows the total percentage of buprenorphine product formulations injected by SKIP respondents indicating any past month injection of buprenorphine to get high.

40% of respondents in the RAPID interviews indicated they had used both buprenorphine and methadone for the purpose of treating or preventing withdrawal sickness, either under a doctor's care or on their own initiative as a self-directed pharmacotherapy for opioid dependence. When asked which drug they preferred, 61.5% chose buprenorphine compared to just 25.6% favoring methadone (9.3% had no preference). Reasons given for the preference of buprenorphine included "lasts longer", "methadone is worse to come off of," and "does not get me high". As one respondent noted:

Methadone made me feel high just like the meds I was trying to come off of where the suboxone just makes me feel normal. On methadone I wanted to sleep all the time and the suboxone I don't. Also I felt the methadone clinics were legal drug dealers who didn't care about anything but the money I was paying them. My suboxone doctor actually cares about me and how I'm doing in my recovery and what's going on in my life.

Our data also indicate that lack of access to a buprenorphine treatment program could be an important factor in the unsupervised use of buprenorphine to treat opioid dependence. For example:

Before I started my treatment program I had a friend get a script, he sold me a couple [buprenorphine] to try and see if they would ease my withdraw. They did, so the next day I called his doctor and tried to get an appointment, the wait was over a month. I ended up going into a traditional treatment program about a week later where they tried to just control the symptoms and it was hell for more than 2 weeks before I finally called the suboxone doc back and basically begged my way in their office.

3.5. Buprenorphine formulations

Fig. 3A shows the misuse of buprenorphine subdivided by formulation type. In the first quarter of 2010 (the earliest date for which data were available), Suboxone® (buprenorphine + naloxone) tablets were the overwhelming choice, with over 90% of buprenorphine users in the past month selecting them. Coincident with the discontinuation of the combination tablet and the introduction of the combination oral film, misuse of the tablet decreased and the misuse of the oral film increased sharply. Very substantial increases in single ingredient (e.g., subutex) tablets misuse also occurred. Buprenorphine patches and solutions were rarely endorsed as drugs of misuse.

3.6. Intravenous injection of buprenorphine

Over one-third (34.4%, $n = 461$) of buprenorphine misusers in the SKIP sample indicated they had injected it in the month prior to treatment. This was particularly prevalent in those misusing both prescription opioids and heroin: 71.1% of those who injected buprenorphine had also used heroin in the past 30 days. As shown in Fig. 3B, single ingredient tablets were the most commonly injected (61.8%), but a surprisingly high number injected the buprenorphine + naloxone tablet (43.6%) or oral film (32.1%). Given that naloxone should have antagonized the euphorogenic effects of buprenorphine, providing a low quality high, we asked RAPID participants how they circumvented the barriers of this formulation. Participants reported a number of simple and easy methods, unethical to specify in this paper, which they believed separated buprenorphine from naloxone, resulting in what they termed "pure buprenorphine" for injection.

3.7. Other motivations for buprenorphine use

Nearly 70% of RAPID follow-up participants indicated that they had used buprenorphine, for any reason, at some point in the past. As shown in the response to the True-False questions in Table 2, very few individuals indicated that they used buprenorphine

Table 2
Motivations for prior buprenorphine use outside of a treatment program.

	RAPID ($n = 106$)
"I have used Buprenorphine at least once. . ."	
Because it gives me a better high than other prescription opioid drugs	2.9
Because it was my drug of choice to get high with	3.9
To maintain my abstinence from other drugs	62.9
Because I was trying to wean myself off drugs on my own	54.8
To hold me over during work/social events	52.9
Because I knew I would not have access to other drugs for a period of time	59.6
Because it was cheaper than other drugs	15.4
Because my drug of choice to get high with was not available	60.4
Because it was the only drug that was available	53.9
To treat my bodily pain when other drugs were unavailable	50.0
Because it helped treat anxiety, depression or other psychological symptoms	33.0

because it produced a better high than other opioids. These data are consistent with our observations in the much larger SKIP sample where very few individuals listed buprenorphine as their drug of choice (Table 1). The primary reasons given for using buprenorphine seem to be divisible into two main categories: (1) use of buprenorphine for the express purpose of treating/preventing withdrawal sickness; and (2) as a substitute to get high when other, more preferred drugs were unavailable (Table 2). Several responses to our open-ended question asking why participants used buprenorphine illustrate these often interrelated points:

When I first took [buprenorphine] I was mainly shooting heroin . . . and then used subutex to keep me from getting sick until I'd use again. Sure the thought of actually using it to get off heroin crossed my mind but I began to use it to get high as well.

I have taken buprenorphine in the past to wean off heroin, both under and not under the care of a physician. I also used it when actively using to keep from getting sick if I did not have enough heroin, and as a substitute.

3.8. Co-morbidity and buprenorphine use

A somewhat surprising finding was that 50% of buprenorphine users indicated treating pain was one of the many reasons for using it (Table 2). A third of the sample also indicated they used buprenorphine to help with psychiatric problems. These points are underscored by the following quotes:

I had some left over from my doctor (who I was no longer seeing) and had some horrific pain in my back that my Norco didn't touch so I decided to go back and use Suboxone.

To get high, to get off opioid, to control physical pain, to numb emotional pain, to avoid withdrawal, to avoid facing life without the safety of a fog, to make uncomfortable situations tolerable, to make unsafe situations feel safe, I used it just like I used opioid—to face a reality I had no idea how to live in.

4. Discussion

Our results demonstrate that the misuse of buprenorphine has increased substantially in the last 5 years, confirming and extending earlier reports of such increases (Drug Enforcement Administration, 2009; Substance Abuse and Mental Health Services Administration and Drug Abuse Warning Network (DAWN), 2011; United States Department of Justice and National Drug Intelligence Center (NDIC), 2011; Wish et al., 2012; Lavonas et al., 2014). Certainly, much of this increase has been fueled by an increase in the therapeutic use of buprenorphine, which was accelerated by the release of generics in 2009. Given that it has been shown that there is a direct correlation between the extent of therapeutic use and diversion to street use (Cicero et al., 2007a,b; Lavonas et al., 2014), increases in buprenorphine misuse are not unexpected. However, our quantitative and qualitative data suggest that another major reason buprenorphine misuse has increased in recent years is due to the fact that it serves a variety of functions for the opioid-abusing population: to get high, manage withdrawal sickness, as a substitute for more preferred drugs, to treat pain, manage psychiatric issues (i.e., depression and anxiety) and as a self-directed treatment to wean off other misused opioids. This is especially evident when viewed in the context of the rise in heroin use in the same time frame which, at least in part, seems to be related to the introduction of an abuse-deterrent formulation of OxyContin®. While this greatly reduced OxyContin's popularity as a drug of abuse, it appears to have been followed by a concomitant increase in both heroin and buprenorphine use. The reasons buprenorphine misuse

has increased so sharply in the past five years, particularly among heroin users, are not fully understood, but may be reflective of three factors.

First, while it is clear that buprenorphine was very rarely the drug of choice, our data indicate that it was an acceptable alternative for getting high when more preferred drugs were unavailable (e.g., cost, lack of supply), particularly in intravenous injection drug users.

Second, aside from the use of buprenorphine to get high, its long half-life makes it ideal to ward off opioid withdrawal sickness until preferred drugs are available or as a self-directed treatment to detox and wean off opioids.

Self-medication, rather than entry into a treatment program, may be related to lack of access or cost of these programs. In this context, our study participants preferred buprenorphine to methadone by more than a 2:1 margin when asked specifically about its efficacy in treating withdrawal sickness. Given that methadone is readily available on the street, access is unlikely to be a factor. Rather it would appear that methadone has more undesirable properties such as side effects, social stigma associated with stand-alone treatment clinics and difficulty in weaning off it.

Finally, our data also suggest that pain management and self-medication of serious psychiatric problems are clearly motivating factors in the use of buprenorphine. Over 50% of our sample indicated that buprenorphine was useful to help them manage their pain and over a third used it to “numb their emotional pain.” These data reinforce the construct that substance abuse is a disorder that rarely exists as a stand-alone entity, but often represents a coping mechanism to treat physical and emotional issues.

Why heroin users are more inclined to use buprenorphine than those who exclusively use prescription opioids is not completely clear, but may be related to our finding that unadulterated buprenorphine is, of course, available in the single ingredient tablet and easily can be extracted from the more common and accessible formulation, buprenorphine + naloxone, making it suitable for injection, a route preferred by many heroin users. In contrast, most other opioids readily available on the street contain acetaminophen, which addicts generally tend to avoid for safety concerns (i.e., liver damage) and the fact that acetaminophen makes these compounds unusable for intravenous injection (Cicero et al., 2013). An additional factor which may favor the use of buprenorphine by those who prefer or use heroin regularly is that the immediacy and intensity of withdrawal is much greater in heroin addicts than prescription drug users and, given the medical complications in these individuals, efforts to wean themselves off heroin using buprenorphine may be more intense than for prescription opioid users. Obviously, these suggestions are speculative and more direct studies should be carried out to examine this.

In 2011, the company marketing buprenorphine + naloxone tablets, under the brand name Suboxone®, argued that the tablet was inherently unsafe due to pediatric exposure and withdrew it from distribution. As a replacement, they introduced an oral film as a safer alternative, which perhaps not coincidentally also extended their patent exclusivity. Although Lavonas et al. (2014) reported that the film has reduced child exposure as reflected in poison control center calls, our data indicate it is misused as readily as the original buprenorphine + naloxone formulation indicating that, at least in terms of use to get high, the delivery device – film or tablets – may be irrelevant for those seeking buprenorphine. The larger question is whether the addition of naloxone to the buprenorphine in the combination product actually discouraged use to get high. On the one hand, those who injected it did extract the buprenorphine from the combination product to remove the naloxone which apparently blunted the euphoric effect. However, oral users did not bother to go through the steps of extraction, and apparently did get some euphoric effect albeit one likely less in quality.

There are limitations to our study which need to be noted. A treatment sample may not be representative of those using opioids “recreationally” or of the racial and gender composition of all opioid users. In addition, like all self-administered surveys, there are the usual problems involving ambiguous response and the inability to ask follow-up questions for clarification. Mitigating this problem, to some extent, is the qualitative data provided by our interviews with study participants which allowed much more in-depth analysis of responses and information not covered in the SKIP survey. Finally, the absence of exposure data does not allow an estimate of the correlation between therapeutic exposure and abuse in the current paper, which could be useful, but this topic has been covered in our earlier work (Lavonas et al., 2014), which supports the association of increases in misuse as a function of increases in exposure.

Role of funding source

The national data were collected as part of the Survey of Key Informants' Patients (SKIP) Program, a component of the RADARS® (Researched Misuse, Diversion and Addiction-Related Surveillance) System, funded through an unrestricted research grant sponsored by Denver Health and Hospital Authority (DHHA), which collects subscription fees from 14 pharmaceutical firms. The interview-driven Research and Patients Interacting Directly (RAPID) Program received support from both DHHA and private university funds.

Contributors

Author Cicero designed the study and wrote the protocol. Author Ellis performed data analysis and research coordination. All authors participated in reviewing the data and drafting the manuscript.

Conflict of interest statement

Authors Cicero and Surratt serve as consultants on the Scientific Advisory Board of the non-profit post-marketing surveillance system, RADARS®. All other authors declare they have no conflict of interest.

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