Drug and Alcohol Dependence xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

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

Theodore J. Cicero[a,*], Matthew S. Ellis[a], Hilary L. Surratt[b], Steven P. Kurtz[b]

[a] Washington University, Department of Psychiatry, Campus Box 8134, 660 S. Euclid Avenue, St. Louis, MO 63110, United States
[b] Nova Southeastern University, Center for Applied Research on Substance Use and Health Disparities, 2 NE 40th Street, Suite 404, Miami, FL 33137, United States

ARTICLE INFO

Article history:
Received 31 March 2014
Received in revised form 2 June 2014
Accepted 3 June 2014
Available online xxx

Keywords:
Buprenorphine misuse, Heroin, Opioid misuse, Self-treatment of opioid dependence

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 buprenorphinehas 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 euphorigenic 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.

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-Trecan 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 Eissenberg, 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

* Corresponding author. Tel.: +1 314 362 4516; fax: +1 314 362 5630.
E-mail address: Cicerot@wustl.edu (T.J. Cicero).

http://dx.doi.org/10.1016/j.drugalcdep.2014.06.005
0376-8716/

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-Martgift 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 (±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.

Please cite this article in press as: Cicero, T.J., et al., Factors contributing to the rise of buprenorphine misuse: 2008–2013. Drug Alcohol Depend. (2014), http://dx.doi.org/10.1016/j.drugalcdep.2014.06.005