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Abuse and diversion of buprenorphine sublingual tablets and film

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ABSTRACT

Buprenorphine abuse is common worldwide. Rates of abuse and diversion of three sublingual buprenorphine formulations (single ingredient tablets; naloxone combination tablets and film) were compared. Data were obtained from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Poison Center, Drug Diversion, Opioid Treatment (OTP), Survey of Key Informants' Patients (SKIP), and College Survey Programs through December 2012. To control for drug availability, event ratios (rates) were calculated quarterly, based on the number of patients filling prescriptions for each formulation ("unique recipients of a dispensed drug," URDD) and averaged and compared using negative binomial regression. Abuse rates in the OTP, SKIP, and College Survey Programs were greatest for single ingredient tablets, and abuse rates in the Poison Center Program and illicit diversion rates were greatest for the combination tablets. Combination film rates were significantly less than rates for either tablet formulation in all programs. No geographic pattern could be discerned.

1. Introduction

Buprenorphine sublingual formulations are approved in the United States (US) for the treatment of opioid dependence (FDA, 2002). Buprenorphine therapy improves retention in substance abuse treatment, decreases emergency department utilization and high-risk sexual behaviors, and improves overall quality of life (Maremmani, Pani, Pacini, & Perugi, 2007; Schwarz, Zelenev, Bruce, & Altice, 2012; Sullivan et al., 2008). Buprenorphine is a long-acting partial agonist of the μ-opioid receptor, a full κ-receptor antagonist, and an ORL-1 partial agonist (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). Buprenorphine exhibits a ceiling agonist effect at high doses, and because of its high affinity for the μ-receptor buprenorphine can interfere with the binding of pure μ-agonists, such as morphine. Because of this, concurrent use of buprenorphine blocks the "high" ordinarily received from abuse of high-potency opioid agonists, such as hydromorphone, and early studies suggested that abuse liability was low by the sublingual route (Walsh & Eissenberg, 2003).

Sublingual buprenorphine is available in the US in three formulations. The single ingredient and naloxone combination tablet formulations were introduced in the US in January 2003, and a mucoadhesive combination film formulation was introduced in September 2010. In the combination tablets and film, naloxone is incorporated in a fixed ratio (1 mg naloxone per 4 mg buprenorphine) to deter abuse by parenteral routes, such as nasal insufflation ("snorting") or injection (Fudala & Johnson, 2006; Mendelson & Jones, 2003). Although use for off-label indications has been described, the most common and only approved use of buprenorphine sublingual formulations in the US is for office-based treatment of opioid dependence, an indication for which its overall safety and effectiveness has been established (Amass et al., 2004; Fiellin & O'Connor, 2002; Johnson, Jaffe, & Fudala, 1992; Mattick, Kimber, Breen, & Davoli, 2008). In the final quarter of 2012, approximately 750,000 patients

Abbreviations: CI, 95% Confidence interval; FDA, United States Food and Drug Administration; IRB, Institutional review board; OTP, Opioid Treatment Program; REMS, Risk evaluation and mitigation strategy; SKIP, Survey of Key Informants' Patients; URDD, Unique recipients of a dispensed drug; US, United States.

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filled prescriptions for buprenorphine in the US (IMS Health Solutions, unpublished data). Generic formulations of single ingredient buprenorphine tablets have been available in the US since late 2009, and combination tablets since February 2013.

Data from several US sources demonstrate that buprenorphine sublingual formulations are diverted and utilized outside of an established physician–patient relationship, both for self-medication of withdrawal symptoms and to produce euphoria (Daniulaityte, Falck, & Carlson, 2012; Yokell, Zaller, Green, & Rich, 2011). To date, few studies have directly compared abuse and diversion rates of buprenorphine single ingredient and combination tablet formulations, and abuse and diversion rates for the combination film have not been reported (Comer & Collins, 2002; Dasgupta et al., 2010; Johanson, Arfken, di Menza, & Schuster, 2012).

The purpose of this study was to measure and compare rates of diversion and abuse of the three formulations of sublingual buprenorphine available in the US.

2. Materials and methods

2.1. Data source

Data were obtained from five programs of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System, as described below. Methods of the RADARS System and its component programs have been described previously (Inciardi et al., 2009). In all RADARS System Programs, data about substance abuse and diversion are collected to the level of the specific formulation and manufacturer, including generic manufacturers, and rates are calculated quarterly.

2.1.1. Poison Center Program

The RADARS System Poison Center Program measures reports to poison centers involving people exposed to prescription opioid and stimulant medications. Fifty of the 57 poison centers operating in the US during the study period participated in the Poison Center Program, and 90.2 percent of the US population (excluding residents of Puerto Rico) resided in a covered area. Calls are initiated to poison centers by health care professionals or the general public, generally because of an acute medical event. Certified specialists in poison information collect data using narrative case notes and standardized data fields with definitions established by the American Association of Poison Control Centers (AAPCC, 2007). De-identified case-level data are transmitted to the RADARS System Poison Center Program, where research staff perform data integrity checks using standardized methods (Winter et al., 2012), and feedback is provided to improve data accuracy (Winter et al., 2013). The RADARS System Poison Center Program began collecting buprenorphine data in October, 2010.

For this analysis, only calls for which the reason for exposure was intentional abuse ("an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect, or some other psychotropic effect") were included. A secondary analysis was performed on a subset of these patients for whom the route of exposure was "parenteral" (defined as, "an exposure resulting from the injection of a substance into the body") or "inhalation/nasal."

2.1.2. Drug Diversion Program

The RADARS System Drug Diversion Program measures illicit diversion by collecting reports of new police investigations, such as forged prescriptions, street drug "buys," and pharmacy robberies, from law enforcement agencies. Approximately 260 police agencies in 49 states and the District of Columbia participate in the Drug Diversion Program. The RADARS System Drug Diversion Program began collecting buprenorphine data in October, 2010.

2.1.3. Treatment programs (Opioid Treatment Program and Survey of Key Informants' Patients Programs)

In the RADARS System Opioid Treatment Program (OTP) and Survey of Key Informants' Patients Program (SKIP), patients entering substance abuse treatment who choose to participate complete a 2-page survey about their substance abuse history. Abuse events are captured by asking subjects to report all opioid medications, "Used in [the] past month to get high." Patients participating in the OTP and SKIP programs are predominately white (56%) male (52%) young adults (median age 31 years (interquartile range: 26–39 years)). During the study period, 83–86 percent of eligible patients chose to participate in the SKIP and 90–95 percent of eligible patients in the OTP. Approximately 79 federally certified treatment programs in 34 states participate in the OTP, and 125 treatment practices in 50 states participate in the SKIP. Data from the OTP and SKIP programs were combined for this analysis.

The primary analysis was performed on all abuse endorsements, and a secondary analysis was performed limiting data to cases in which the patient endorsed buprenorphine abuse by injection. The treatment programs began collecting buprenorphine data in April 2011.

2.1.4. College Survey Program

The RADARS System College Survey Program is an online questionnaire collecting data from self-identified students attending a 2- or 4-year college, university or technical school at least part-time during the specified sampling period. Data from approximately 2,000 participants are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer. Each sample is equally distributed across the four geographic regions of the United States (W, NW, S, and NE) and is composed of self-identified students who have agreed to be contacted to complete online surveys. Cases are defined as self-reported non-medical use of prescription opioid or stimulant medication by college students in the previous academic semester/quarter or over the summer break. Although non-medical use is not strictly synonymous with abuse (for example, using a roommate's oxycodone to treat pain from a sports injury is non-medical use but not abuse), in the vernacular of this report the terms are used interchangeably. Cases are assigned to the reported 3-digit ZIP code of the college student's residence. The College Survey Program began collecting buprenorphine data with the spring term 2011 survey.

2.2. Rate calculations

In order to account for differences in the availability of different drug formulations in the community, event ratios (rates) were calculated based on the number of persons filling prescriptions ("unique recipients of a dispensed drug," URDD). One URDD is a single person filling a prescription for a specific product in a 3-digit zip code area covered by a RADARS System program in a year-quarter. Sales data used to calculate URDD were purchased from IMS Health Solutions (Parsippany, NJ). A complete description of URDD and the method by which URDD data are used to calculate rates have been published previously (Dasgupta et al., 2010; Smith et al., 2007). In order to provide context about changing prescribing of the three buprenorphine formulations over the study period, national-level URDD data were compared with population data from the US Census Bureau, using linear interpolation to produce quarterly data between available population data points.

Program event rates for each of the three formulations were calculated quarterly, and the averages of these rates, calculated using negative binomial regression, were used for the primary analysis. For each RADARS System program, the time period for analysis began during the first year/quarter for which buprenorphine data were collected and ended in the final quarter of 2012. Thus, the primary analysis contains 27 months of data in the Poison Center and Drug Diversion Programs, 21 months of data in the treatment programs, and 6 terms of data (approximately 18 months of sampling period