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Understanding abuse of buprenorphine/naloxone film versus tablet products using data from ASI-MV® substance use disorder treatment centers and RADARS® System Poison Centers

Stephen F. Butler [a,*], Ryan A. Black [a,b], Stevan Geoffrey Severtson [c], Richard C. Dart [c,d], Jody L. Green [c]

[a] Inflexxion, Inc., Newton, MA, USA
[b] Center for Psychological Studies, Nova Southeastern University, Fort Lauderdale, FL, USA
[c] Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO, USA
[d] University of Colorado School of Medicine, Aurora, CO, USA

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ABSTRACT

Objectives: The objectives were to examine the abuse prevalence and route-of-administration (ROA) profiles of sublingual buprenorphine/naloxone combination (BNX) film in comparison with the BNX tablet and to identify clinically-relevant subgroups of patients or geographic patterns.
Methods: Between Q1 2015 through Q3 2015, data were collected from two major surveillance systems: (1) assessment of individuals in substance use disorder (SUD) treatment collected from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) ASI-MV® system and (2) intentional abuse/misuse exposures in the RADARS® System Poison Center Program. Poisson regression models were tailored to each system's data characteristics by population (all SUD treatment patients, US census) and adjusted for prescription volume. Effects of gender, race, age and US region as well as ROA profile were examined.
Results: For the ASI-MV study, 45,695 assessments of unique adults evaluated for substance use problems were collected. The abuse rate unadjusted for prescription volume of BNX tablet formulation was 2.64 cases/100 ASI-MV respondents versus 7.01 cases for the film formulation (RR = 0.390, $p < 0.001$). Prescription-adjusted abuse, however, was greater for the tablet version (0.47 abuse cases/100 ASI-MV respondents/100,000 dosage units compared with 0.38 for the film) (RR = 1.25, $p < 0.001$). Results among the US population from the RADARS System Poison Center Program data revealed a similar pattern; population rates for film abuse (0.0364) were greater than for tablet (0.0161), while prescription-adjusted rates were greater for tablet (0.2114) than for film (0.1703) per 100,000 prescriptions. ASI-MV ROA analyses indicated less abuse of the film by any alternate route, insufflation or injection than the tablet. Poison center data found more injection of tablets than film, although insufflation was not significantly different.
Conclusions: On a prescription-adjusted basis, overall abuse of the BNX tablet is greater than that of the sublingual film formulation. For those who continue to abuse BNX, use by alternate ROAs was, in general, lower for the film.

1. Introduction

The use of medication-assisted treatment (MAT) is considered an integral contributor to recovery in patients with opioid use disorder when used with adequate coordination of psychosocial treatments (The American Society of Addiction Medicine, 2014). Reviews of MAT have revealed generally positive impacts on treatment retention and reduction of illicit opioid use for both methadone (Fullerton et al., 2014) and buprenorphine (Thomas et al., 2014). This paper examines post-marketing data to compare the abuse prevalence and route-of-administration (ROA) profiles of two forms of buprenorphine/naloxone combination (BNX) products commonly used in MAT, the tablet formulation and the sublingual film.

In 2003, buprenorphine sublingual formulations were approved in the United States for office-based treatment of opioid dependence and have been shown to be safe and effective (Mattick, Breen, Kimber, & Davoli, 2014) in a mono-product version and a buprenorphine/naloxone combination tablet formulation. A 4:1 combination of buprenorphine and naloxone was expected to reduce abuse of the product by non-oral routes of administration, particularly insufflation (snorting) and injection (Fudala & Johnson, 2006; Mendelson & Jones, 2003). In 2010, a sublingual combination (BNX) film formulation was introduced. Early investigations (Lintzeris et al., 2013) suggested this formulation adhered to the sublingual mucosa quickly, dissolved more

* Corresponding author at: Inflexxion, Inc., 890 Winter St., Ste. 235, Waltham, MA 02451, USA.
E-mail address: sfbutler@inflexxion.com (S.F. Butler).

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rapidly in the mouth, and hence may require less time for supervised dosing compared to the tablet formulation. It was also presumed to more effectively reduce intentional removal of doses by patients for diversion or for injection. Based on this reasoning, Lintzeris et al. (2013) suggested the film formulation may be an example of an abuse deterrent opioid formulation.

Since its introduction as a treatment option for individuals with opioid use disorder, the amount of prescribed buprenorphine has increased, along with reports of diversion and abuse of buprenorphine (Cassidy, DasMahapatra, Black, Wieman, & Butler, 2014; Dasgupta et al., 2010). Studies comparing relative abuse rates have yielded conflicting evidence. For instance, a comprehensive study comparing the sublingual tablets and film across several post-marketing data streams (Lavonas et al., 2014) suggested that the number of persons filling prescriptions ("unique recipients of a dispensed drug," or URDD) for the BNX film increased markedly, while the number filling prescriptions for the tablet version has diminished. In that study, however, abuse rates per 10,000 URDD were higher for the BNX tablet formulation than for the film across data sources, including poison center data, data from a drug diversion reporting program, surveys of individuals in the RADARS System Opioid Treatment and Survey of Key Informants' Patients Programs, and the RADARS System College Survey Program (Lavonas et al., 2014). Examination of average rates of abuse by non-oral routes (i.e., insufflation and injection) measured within the poison center data stream, opioid treatment programs and other SUD treatment data, found significantly lower prescription-adjusted rates for insufflation and injection associated with the film (0.2 per 10,000 URDD for insufflation and 1.3 per 10,000 URDD for injection) than both the buprenorphine mono-product tablet (0.6 per 10,000 URDD for insufflation and 27.0 per 10,000 URDD for injection) and BNX tablet (0.8 per 10,000 URDD for insufflation and 3.3 per 10,000 URDD for injection) formulations ($p < 0.001$ for all comparisons).

A study in Australia examined diversion and injection rates and routes for the buprenorphine mono-product, the BNX tablet and film, as well as for methadone (Larance et al., 2014). The results differed from those observed in the US study (Lavonas et al., 2014) in that they found "no evidence that the BNX film is superior to the BNX tablet in reducing non-adherence and diversion" (p.26) (Larance et al., 2014). Specifically, the Australian study found that injection rates of BNX film were not different from BNX tablet, buprenorphine mono-product or methadone in a population of 544 individuals in opioid substitution therapy. However, "weekly or more frequent" (p.26) (Larance et al., 2014) injection was lower for film (3%) than the single-entity version (11%) but injection of film was similar to injection of BNX tablets (9%) and methadone (3%). In another sample, reported in the same paper, of 541 persons who inject drugs regularly, subjects reported less recent injection of BNX film than comparators, but after adjusting for availability, injection rates were similar to the BNX tablet and methadone (Lavonas et al., 2014).

The differences in the population and methods of the US and Australian studies make direct comparison of these results difficult. The focus of the Australian study (Larance et al., 2014) was on injection of the products as the primary outcome, and one of their groups in particular was defined as persons who inject drugs (PWID). The US study (Lavonas et al., 2014), however, utilized multiple data streams, focused on various measures of abuse in different populations, and examined injection route in the poison center data and substance treatment center data. In both of these data sets, prescription-adjusted rates of injection for the film were observed to be lower than for the BNX tablet.

The present study examines prescription opioid abuse using data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®), as well as from the RADARS® System. The primary objective was to further understand abuse patterns of the sublingual BNX film in comparison with BNX tablet formulation with respect to abuse prevalence and route-of-administration profile. An additional objective was to determine, whether product-specific ROA data from SUD treatment settings could clarify the apparent discrepancy between the US study (Lavonas et al., 2014) and the Australian study (Larance et al., 2014).

The current study examined the previous 30-day self-reported abuse rates of BNX film and BNX tablet among individuals evaluated in a substance-use treatment context using several denominators; the study also provided an in-depth comparison of use by alternate routes of administration (i.e., other than oral/sublingual route). In addition to the NAVIPPRO SUD treatment data, intentional abuse and misuse exposures from the RADARS System Poison Center Program reported for BNX film and BNX tablets, as well as ROA profiles for the two BNX formulations, were examined during the same timeframe as the NAVIPPRO data and using methods similar to those utilized in the earlier RADARS study (Lavonas et al., 2014).

2. Methods

2.1. Data sources

2.1.1. Substance use disorder (SUD) treatment data

The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) surveillance system provides real-time monitoring of patterns and trends of prescription medication use and abuse for pharmaceutical companies and other public health stakeholders. NAVIPPRO conducts ongoing surveillance and epidemiological studies for FDA-regulated products that are addictive and pose health risks. Data on specific products and routes of administration (ROA) allow evaluation of the risk profile of a given opioid product in relation to comparator products.

Substance use treatment center data for this study were obtained from a sample of adults, aged 18 years and older, assessed for substance use problems and treatment-planning using the Addiction Severity Index-Multimedia Version (ASI-MV) (Butler et al., 2008) between Q1 2015 through Q3 2015. The ASI-MV is a structured, self-administered, computerized interview that provides for the clinician a standardized assessment of the severity of a range of problem areas typically associated with drug and alcohol abuse (Butler et al., 2001; Hendricks, Kaplan, VanLimbeek, & Geerlings, 1989; Kosten, Rounsaville, & Kleber, 1983; McLellan et al., 1992). When a patient indicates any use of a prescription opioid in the previous 30 days, the ASI-MV captures data related to past 30-day use and abuse for >60 brand and generic prescription opioid products, including information on ROA used and sources of procurement for each product. When a respondent has completed the assessment locally at the treatment site, individual-level data are de-identified and electronically uploaded to a central server where they are available for analysis (Butler et al., 2008). This data stream has been employed widely to evaluate the relative abuse potential of various products and drug compounds, as well as to compare ROA profiles among specific products and compounds (Butler et al., 2013; Butler, Black, Cassidy, Dailey, & Budman, 2011; Cassidy et al., 2014; Cassidy et al., 2015; Chilcoat et al., 2015). Since ASI-MV data are collected primarily for clinical purposes, analyses of de-identified aggregate data for research purposes have been determined to be exempt from IRB review by the New England Institutional Review Board (NEIRB).

In order to use a consistent timeframe across both the ASI-MV SUD treatment dataset and the RADARS System Poison Center Program dataset, the timeframe selected for both datasets started in Q1 2015, since the buprenorphine/naloxone film was added as a separate selection to the ASI-MV in January 2015. Approximately 15,000 cases are added to the ASI-MV data stream each quarter, so it was determined that three quarters would provide sufficient power for the ASI-MV to detect meaningful differences across the two formulations (BNX film versus BNX tablet). The RADARS System Poison Center Program dataset contains reports on BNX film since that product's introduction, although the present analyses of those data were limited to the three quarters available to the ASI-MV.